IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BOSTON SCIENTIFIC CORPORATION and BOSTON SCIENTIFIC SCIMED, INC., Plaintiffs, v. JOHNSON & JOHNSON, INC., CORDIS CORPORATION, and WYETH Defendants.	Civil Action No. 07-333-SLR Civil Action No. 07-348-SLR Civil Action No. 07-409-SLR
BOSTON SCIENTIFIC CORPORATION and BOSTON SCIENTIFIC SCIMED, INC., Plaintiffs, v. JOHNSON & JOHNSON, INC., CORDIS CORPORATION, and WYETH Defendants.	Civil Action No. 07-765-SLR

NOTICE OF SUBPOENA AND DEPOSITION
(DIRECTED TO DR. GREGORY KOPIA)

TO:

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John G. Day, Esq.
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PLEASE TAKE NOTICE that, pursuant to Rules 30(b)(6) and 45 of the Federal Rules of Civil Procedure, Plaintiffs Boston Scientific Corp. and Boston Scientific Scimed, Inc. (collectively, "BSC") are serving a subpoena ad testificandum and duces tecum upon Dr. Gregory Kopia, in the form appended hereto, for the production of documents described in Exhibit A to the subpoena, and for an oral deposition.

The requested documents are to be produced by 9:00 a.m. EDT on September 10, 2008 at the offices of Young Conaway Stargatt & Taylor LLP, c/o Karen L. Pascale, Esq., The Brandywine Building, 1000 West Street, 17th Floor, Wilmington, DE 19899-0391.

The deposition will take place at the offices of Young Conaway Stargatt & Taylor LLP, The Brandywine Building, 1000 West Street, 17th Floor, Wilmington, DE 19899-0391, commencing at 9:00 a.m. EDT on September 16, 2008.

The deposition will be taken in accordance with the Federal Rules of Civil Procedure before an official authorized to administer oaths under the laws of the United States, and shall continue from day to day until completed. This deposition may be recorded by any means permitted under the Federal Rules of Civil Procedure, including audio, audio-visual, and/or stenographic means.

You are invited to attend and cross-examine.

YOUNG CONAWAY STARGATT & TAYLOR LLP

/s/ *Karen L. Pascale*

August 27, 2008

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on August 27, 2008, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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I further certify that on August 27, 2008, I caused a copy of the foregoing document to be served by e-mail on the above-listed counsel and on the following non-registered participants in the manner indicated:

By E-Mail

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Attorneys for Plaintiffs, Boston Scientific Corporation and Boston Scientific Scimed, Inc.

A 88 (Rev. 11/91) Subpoena in a Civil Case

United States District Court

DISTRICT OF DELAWARE

SUBPOENA IN A CIVIL CASE

BOSTON SCIENTIFIC CORPORATION and
BOSTON SCIENTIFIC SCIMED, INC.,
Plaintiffs,

v.

JOHNSON & JOHNSON, INC., and
CORDIS CORPORATION.
Defendants.

Civil Action No. 07-333-SLR
Civil Action No. 07-348-SLR
Civil Action No. 07-409-SLR

BOSTON SCIENTIFIC CORPORATION and
BOSTON SCIENTIFIC SCIMED, INC.,
Plaintiffs,

v.

JOHNSON & JOHNSON, INC.,
CORDIS CORPORATION, and WYETH
Defendants.

Civil Action No. 07-765-SLR

TO: Dr. Gregory Kopia
58 Longfield Dr
Hillsborough, NJ 08844

PENDING IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

☐ YOU ARE COMMANDED to appear in the United States District Court at the place, date, and time specified below to testify in the above case.

PLACE OF TESTIMONY	COURTROOM
	DATE AND TIME

☑ YOU ARE COMMANDED to appear at the place, date, and time specified below for a deposition in the above case. The deposition may be recorded by sound, sound-and-visual, and/or stenographic means.

PLACE OF DEPOSITION:	DATE AND TIME
Young Conaway Stargatt & Taylor, LLP The Brandywine Building 1000 West Street, 17th Floor Wilmington, DE 19899-0391	September 16, 2008 9:00 AM

☑ YOU ARE COMMANDED to produce and permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects): See attached Exhibit A.

PLACE:	DATE AND TIME
Young Conaway Stargatt & Taylor, LLP c/o Karen Pascale The Brandywine Building 1000 West Street, 17th Floor Wilmington, DE 19899-0391	September 10, 2008 9:00 AM

☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below.

PREMISES	DATE AND TIME

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)	DATE
Michael Levy	8/27/08
ISSUING OFFICER'S NAME ADDRESS AND PHONE NUMBER Michael K. Levy, Attorney for Plaintiffs, Boston Scientific Corporation and Boston Scientific Scimed, Kenyon & Kenyon, One Broadway, New York, NY 10004-1007 212-425-7200	

AO 88 (Rev. 11/91) Subpoena in a Civil Case

PROOF OF SERVICE

	DATE	PLACE
SERVED		

SERVED ON (PRINT NAME)	MANNER OF SERVICE
SERVED BY (PRINT NAME)	TITLE

DECLARATION OF SERVER

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Proof of Service is true and correct.

Executed on
DATE

SIGNATURE OF SERVER

ADDRESS OF SERVER

Rule 45, Federal Rules of Civil Procedure, Parts C & D:

(c) PROTECTION OF PERSONS SUBJECT TO SUBPOENAS.

(1) A party or an attorney responsible for the issuance and service of a subpoena shall take reasonable steps to avoid imposing undue burden or expense on a person subject to that subpoena. The court on behalf of which the subpoena was issued shall enforce this duty and impose upon the party or attorney in breach of this duty an appropriate sanction, which may include, but is not limited to, lost earnings and a reasonable attorney's fee.

(2)(A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of the subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy the materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice tot he person commanded to produce, move at any time for an order to compel the production. Such an order to compel production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3)(A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

(i) fails to allow reasonable time for compliance;

(ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden.

(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial, the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena or, if the party in whose behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

(d) DUTIES IN RESPONDING TO SUBPOENA.

(1) A person responding to a subpoena to produce documents shall produce them as they are kept in the usual course of business or shall organize and label them to correspond with the categories in the demand.

(2) When information subject to a subpoena is withheld on a claim that it is privileged or subject to protection as trial preparation materials, the claim shall be made expressly and shall be supported by a description of the nature of the documents, communications, or things not produced that is sufficient to enable the demanding party to contest the claim.

EXHIBIT A

DEFINITIONS

A) And/Or. The connectives "and" and "or" shall be construed either disjunctively or conjunctively so as to acquire the broadest possible meaning.

B) Any/All/Each. The terms "any," "all" or "each" shall be construed as "any, all and each."

C) Document. The term "document" shall have the broadest meaning permitted by Fed. R. Civ. P. 34(a), and shall include, without limitation, any tangible recordation of information by any means and in any medium, including, but not limited to, information that is handwritten, typewritten, printed, recorded, filmed, stored on computer disks or electronic databases, and/or any other tangible recordation discoverable under the Federal Rules of Civil Procedure that are in your possession, custody, or control or to which you otherwise have access. "Document" further includes, without limitation, the original, any draft, and any non-identical version or copy. Documents having self-stick removable notes shall be produced in a manner so that all material on both the note and the document is legible.

D) Number. The use of the singular form of any word shall include the plural and vice versa.

E) Person. The term "person" shall mean any natural person or any business, firm, association, organization, joint venture, partnership, corporation, or any legal or governmental entity.

F) Concern/Concerning. The term "concern" or "concerning" shall mean comprising, constituting, containing, describing, discussing, embodying, evidencing, identifying,

indicating, involving, referring to, reflecting, relating to, supporting, or otherwise in any way pertaining directly or indirectly to.

G) <u>'7286 Patent</u>. The term "'7286 patent" shall mean U.S. Patent No. 7,217,286, along with the applications from which that patent issued, and any related U.S. or foreign applications. (Attached as Exhibit 1.)

H) <u>'3286 Patent</u>. The term "'3286 patent" shall mean U.S. Patent No. 7,223,286, along with the applications from which that patent issued, and any related U.S. or foreign applications. (Attached as Exhibit 2.)

I) <u>'473 Patent</u>. The term "'473 patent" shall mean U.S. Patent No. 7,229,473, along with the applications from which that patent issued, and any related U.S. or foreign applications. (Attached as Exhibit 3.)

J) <u>'662 Patent</u>. The term "'662 patent" shall mean U.S. Patent No. 7,300,662, along with the applications from which that patent issued, and any related U.S. or foreign applications. (Attached as Exhibit 4.)

K) <u>Cordis Patents</u>. The term "Cordis Patents" shall mean the '7286 patent, the '3286 patent, the '473 patent, and the '662 patent.

L) <u>Sirolimus</u>. The term "sirolimus" shall mean sirolimus or rapamycin, as it is alternatively known, or the drug Rapamune.

M) <u>Drug-Eluting Stent</u>. The term "Drug-Eluting Stent" shall include, without limitation, any stent previously or currently manufactured, used, marketed, sold, offered for sale, or distributed that utilizes any therapeutically active ingredient in or on the stent, or in a polymer on the stent, including any commercial, developmental, working or non-working model, or any prototype of any of the foregoing.

INSTRUCTIONS

A) Where an objection is made to any discovery request or sub-part thereof, the objection shall state with specificity all grounds for the objection.

B) Objection to production of a document is not grounds for refusing to produce other documents called for by the request, the production of which is not objected to. If you object to the production of one or more documents, you shall identify in detail the document(s) whose production is objected to, state the legal grounds for the objection, and produce all other documents for which no objection is made.

C) If any requested document cannot be produced in full, produce the remainder and state whatever information, knowledge, or belief you have concerning the unproduced portion and the reasons for the portion not being produced.

D) Where a claim of privilege is asserted in responding or objecting to any discovery request or sub-part thereof, and information is not provided on the basis of such assertion,

(1) the party asserting the privilege shall in the response or objection to the discovery request or sub-part thereof, identify the nature of the privilege (including work product) which is being claimed and if the privilege is being asserted in connection with a claim or defense governed by state law, set forth the state privilege rule being invoked; and

(2) the following information shall be provided in the objection:

(a) for documents: (i) the identities of the author(s), addressee(s) and recipient(s); (ii) the type of document; (iii) the

general subject matter of the document; (iv) the date of the document; and (v) the location of the document.

(b) for oral communications: (i) the identity of the person making the communication and the identity of all persons present while the communication was made and, where not apparent, the relationship of the persons present to the person making the communication; (ii) the date and place of the communication; and (iii) the general subject matter of the communication.

E) If any document requested to be identified or produced has been destroyed, provide the following additional information as to each such document, (a) the date of destruction of the document, (b) the reason for the destruction of the document, (c) the identification of the person who destroyed the document, and (d) the identification of any person who directed that the document be destroyed.

F) Where documents or things in your possession, custody, or control are requested or inquired of, such request or inquiry includes documents and things in the possession, custody, or control of each of your agents, servants, employees, representatives, and, unless privileged, your attorneys.

G) Each document or group of documents produced in response to a document request shall indicate the number of each and every request to which it is responsive.

H) All documents are to be produced with their original file folders, file jackets, envelopes, or covers, or an accurate reproduction thereof.

I) If an English language version or English language translation of a non-English document exists, both the non-English language document and the English language

version or English language translation of the non-English document should be produced. If a written transcription of an audio and/or video document exists, the written transcription and the audio and/or video document should be produced.

J) These discovery requests are deemed to be continuing. With respect to any of the following discovery requests as to which you, after responding, discover or acquire additional responsive material, BSC requests that you produce such additional material for inspection and copying promptly after you discover or acquire such additional material.

DOCUMENTS AND THINGS TO BE PRODUCED

1. All documents and things concerning the Cordis Patents.

2. All documents and things concerning the subject matter claimed in the Cordis Patents.

3. All documents and things concerning the research, development, characterization or testing of the subject matter claimed in the Cordis Patents, including but not limited to, Drug-Eluting Stents or Sirolimus-eluting coronary stents, and the person(s) involved in the development of a Drug-Eluting Stent or Sirolimus-eluting coronary stent.

4. All documents and things concerning the inventorship of the Cordis Patents.

5. All documents and things concerning the conception of the subject matter in each of the claims of the Cordis Patents.

6. All documents and things concerning the reduction to practice of the subject matter of each claim of the Cordis Patents.

7. All documents and things concerning the best mode of practicing the subject matter of the claims of the Cordis Patents, including but not limited to, Drug-Eluting Stents or Sirolimus-eluting coronary stents.

8. All documents and things concerning any use, publication, patent, patent application or any other reference or conduct that may be material prior art to the Cordis Patents.

9. All documents and things concerning Sirolimus or any analog of Sirolimus.

10. All documents and things concerning the actual or potential use of Sirolimus (or an analog, derivative, or congener thereof) to prevent or treat any vascular condition, including but not limited to, neointimal proliferation, restenosis, atherosclerosis, and smooth muscle cell proliferation.

11. For the time period prior to April 16, 1998, all documents and things concerning the release of a therapeutic agent from a polymer or copolymer over a period of at least one week, including but not limited to, all documents and things concerning any testing related thereto.

EXHIBIT 1

US007217286B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,217,286 B2**
(45) **Date of Patent: *May 15, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

(75) Inventors: **Robert Falotico**, Bell Mead, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/467,035**

(22) Filed: **Aug. 24, 2006**

(65) **Prior Publication Data**

US 2007/0021825 A1 Jan. 25, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,568, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.45–1.48; 427/2.1–2.31
See application file for complete search history.

(56) **References Cited**

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Primary Examiner—Suzette Gherbi
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets

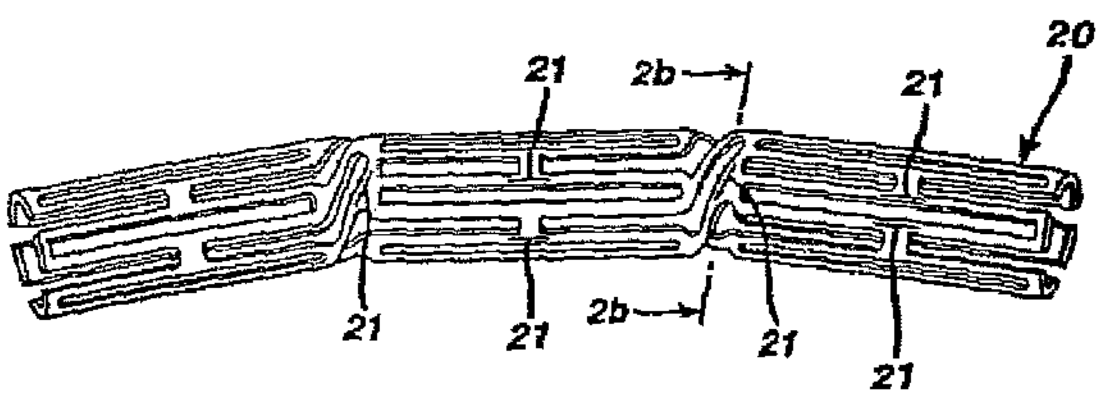

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FIG. 1

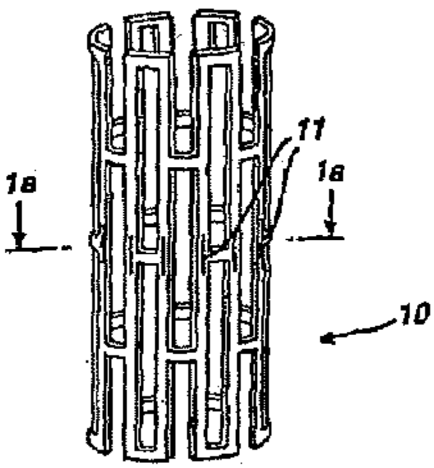


FIG. 1a

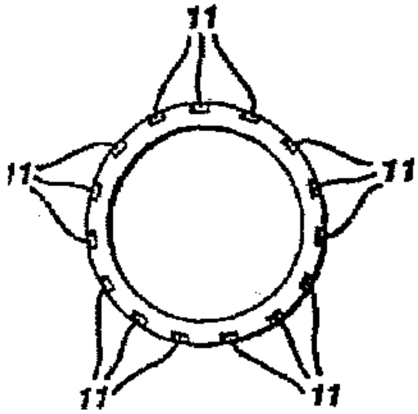


FIG. 2a

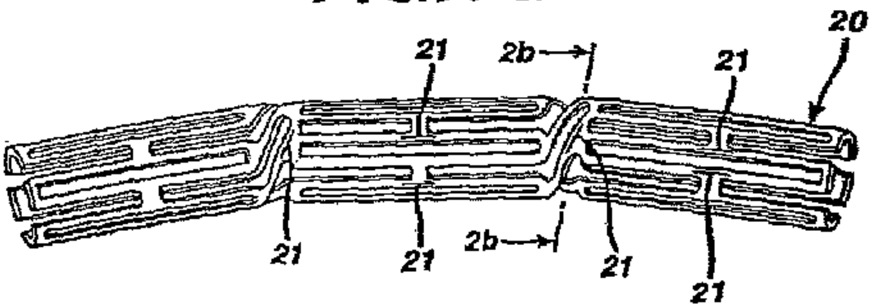


FIG. 2b

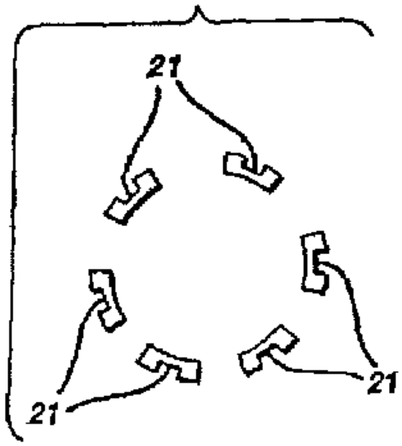


FIG. 3a

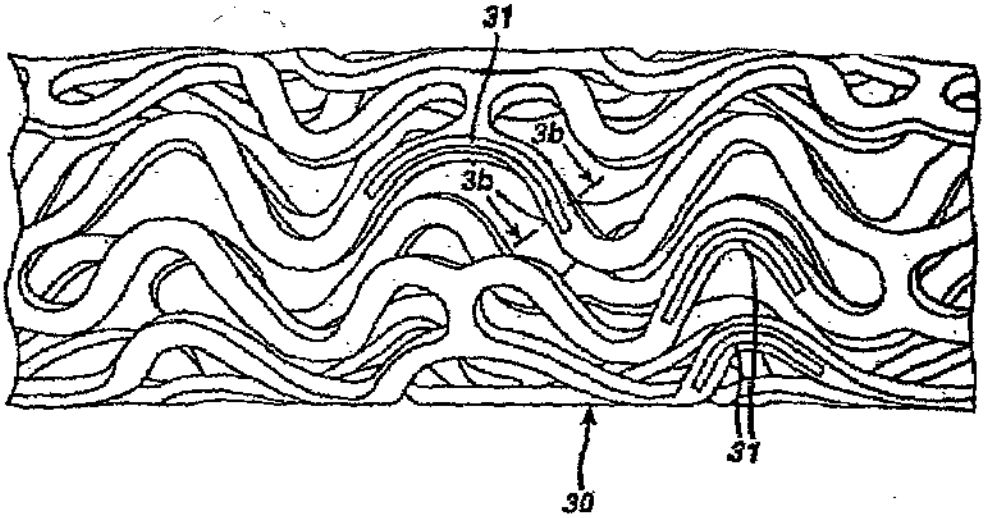


FIG. 3b

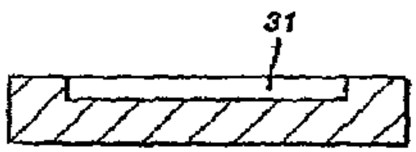
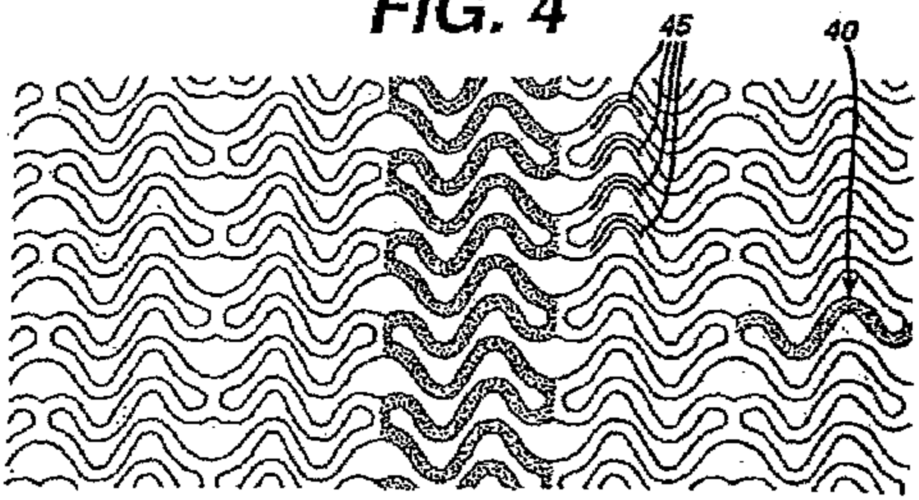


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which in turn is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosures of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon

vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a *contractile* phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF),

etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotype to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca.Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1**A are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. *2a* and *2b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. *3a* and *3b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction

in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412-422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 Nature, 25-626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625–634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611-616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986);. Majesky et al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Natl, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Liu, M. W. et al., 81 Circulation, 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412–417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of

SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

- Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.
- Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.
- or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.
- or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.
- Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.
- Extravascular delivery by the pericardial route.
- Extravascular delivery by the advential application of sustained release formulations.

Uses:

- for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.
- prevention of tumor expansion from stents.
- preventingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolacton-glycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the

stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery Via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A device comprising a metallic stent, a biocompatible, nonabsorbable polymeric carrier, and a therapeutic agent, wherein:

said polymeric carrier comprises an acrylate-based polymer or copolymer, a fluorinated polymer, or a mixture thereof, and

said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, and is present in an amount effective to inhibit neointimal proliferation.

2. The device according to claim 1 wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The device according to claim **1** that provides a controlled release of said therapeutic agent over a period of several weeks.

4. The device according to claim **2** that provides a controlled release of said therapeutic agent over a period of several weeks.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a device according to any one of claims **1** to **4** in the lumen of said coronary artery.

* * * * *

EXHIBIT 2

US007223286B2

(12) **United States Patent**
Wright et al.

(10) **Patent No.: US 7,223,286 B2**
(45) **Date of Patent: *May 29, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

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(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

77 Claims, 2 Drawing Sheets

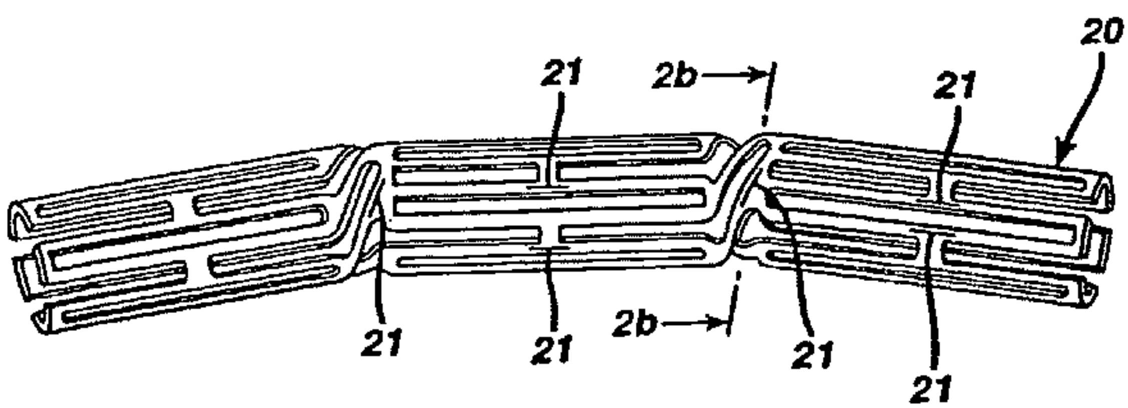

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FIG. 1

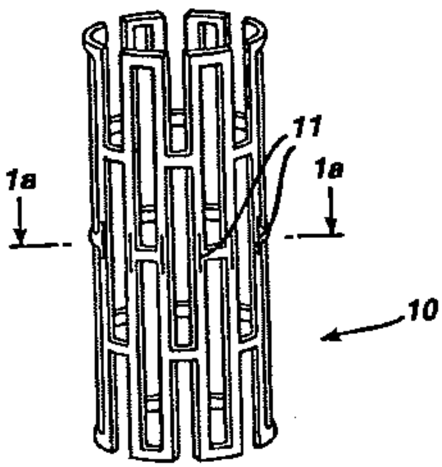


FIG. 1a

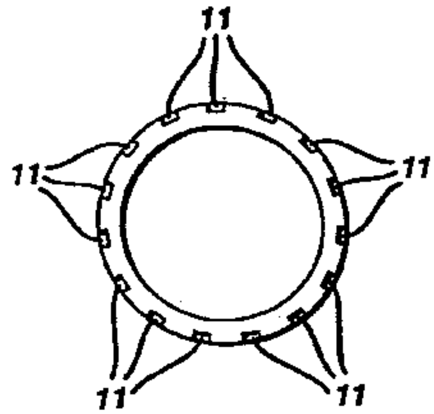


FIG. 2a

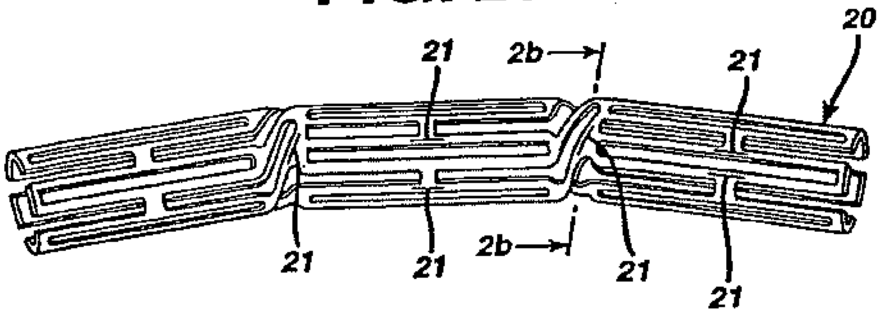


FIG. 2b

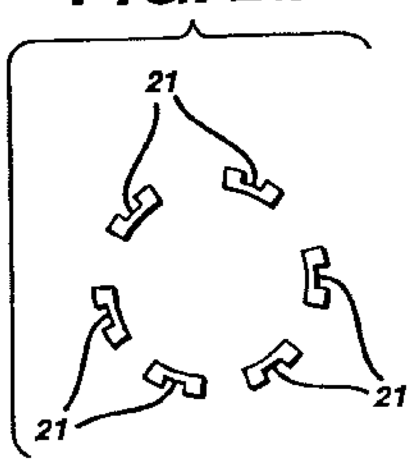


FIG. 3a

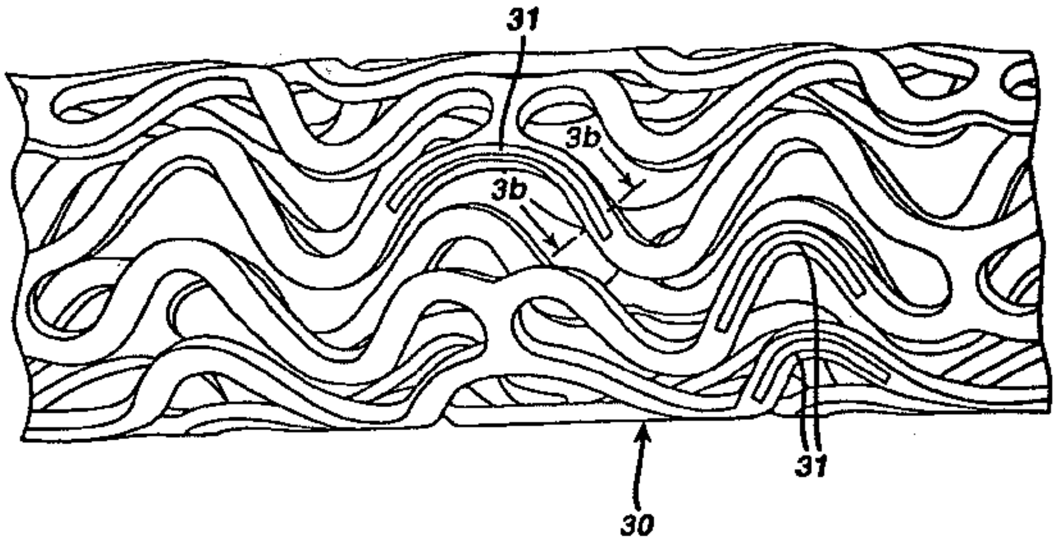


FIG. 3b

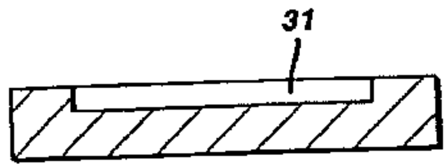
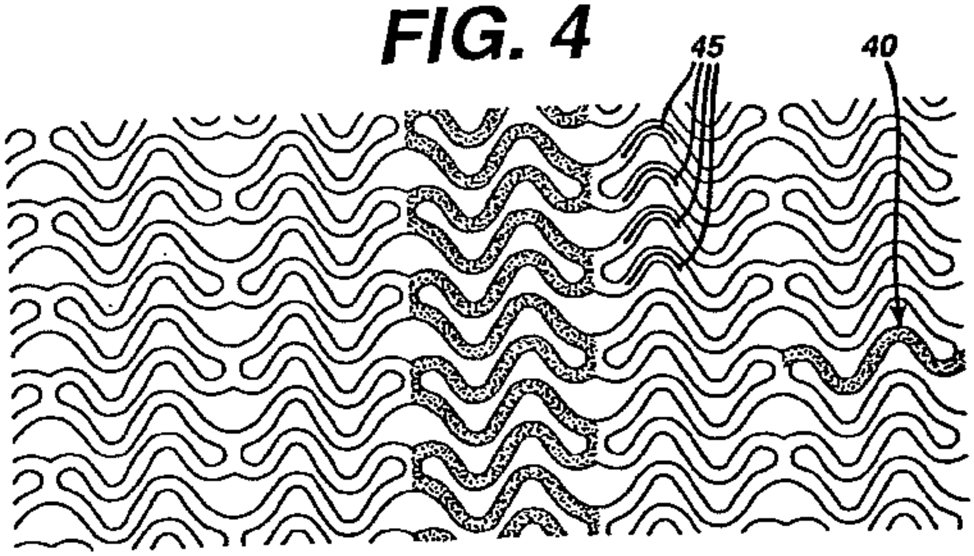


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which in turn is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present understanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth muscle cells (SMC) themselves release cell derived growth factors with subsequent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known but may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellular production of tissue plasminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG)

PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000-300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procedure of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acute reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a 'contractile' phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injured. Cell derived growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC.

These cells undergo a phenotypic change from the contractile phenotyope to a 'synthetic' phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: *Vascular Smooth Muscle Cells in Culture,* Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca Ration, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139–145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which FIGS. **1** and **1A** are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. **2***a* and **2***b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. **3***a* and **3***b* are further alternate figures of a device containing a grooved reservoir; and

FIG. **4** is a layout view of a device containing a reservoir as in FIG. **3**.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 *Circulation,* 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 232–242 (1993); Serruys, P. W. et al., 88 *Circulation,* (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent **10** seen in layout in FIG. **4**, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 93 Circulation, 412–422, (1996). Thus, 1) sustained

mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin and heparin fragments (Clowes and Karnovsky, 265 *Nature,* 25-626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625-634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611-616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839-845 (1986);. Majesky et al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am. J. Pathol., 313-330 (1990); Okada, T. et al., 25 *Neurosurgery,* 92-898, (1989) colchicine (Currier, J. W. et al., 80 *Circulation,* 11-66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186-188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Natl. Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 *Science,* 1129-1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Liu, M. W. et al., 81 *Circulation,* 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 *J. Circulation,* 1266-1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510-518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B-117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110-116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Marx et al. (Circ Res 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277-2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409-1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods:

These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake

Extravascular delivery by the pericardial route

Extravascular delivery by the advential application of sustained release formulations.

Uses: for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolacton-glycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any identified in the first experimental method, is applied to the stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery

A: Polymeric Sheet Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolide) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10μ to 1000μ. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating: Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed is:

1. A stent having a coating applied thereto, wherein said coating comprises a biocompatible polymer/drug mixture and said drug is rapamycin or a macrocyclic lactone analog thereof.

2. A stent according to claim **1** comprising a generally thin walled cylinder containing a plurality of generally solid struts to which said coating is applied.

3. A stent according to claim **2** further comprising a channel formed in at least one of said struts.

4. A stent according to claim **3**, wherein said channel has a closed perimeter on all sides, an open top and a generally rectangular perimeter, and said channel is smaller in all dimensions than said strut.

5. A stent according to claim **1** wherein the coating is dip-coated onto the stent.

6. A stent according to claim **1** wherein the coating is spray-coated onto the stent.

7. A stent according to claim **1** wherein said rapamycin or macrocyclic lactone analog thereof is contained in the coating at a weight percentage of about 30%.

8. A stent according to claim **1** wherein the coating comprises a degradable polymer.

9. A stent according to claim **1** wherein the coating comprises a nonabsorbable polymer.

10. A stent according to claim **1** wherein the coating comprises a lactone-based polyester; a lactone-based copolyester; a polyanhydride; a polyaminoacid; a polysaccharide; a polyphosphazene; a poly(ether-ester) copolymer; a polydimethylsiloxane; a poly(ethylene)vinylacetate; a poly (hydroxy)ethylmethylmethacrylate; an acrylate based polymer; an acrylate based copolymer; a polyvinyl pyrrolidone; a cellulose ester; a fluorinated polymer; or a blend thereof.

11. A stent according to claim **10** wherein the coating comprises a lactone-based polyester.

12. A stent according to claim **10** wherein the coating comprises a lactone-based copolyester.

13. A stent according to claim **10** wherein the coating comprises a polyanhydride.

14. A stent according to claim **10** wherein the coating comprises a polyaminoacid.

15. A stent according to claim **10** wherein the coating comprises a polysaccharide.

16. A stent according to claim **10** wherein the coating comprises a polyphosphazene.

17. A stent according to claim **10** wherein the coating comprises a poly(ether-ester) copolymer.

18. A stent according to claim **10** wherein the coating comprises a polydimethylsiloxane.

19. A stent according to claim **10** wherein the coating comprises a poly(ethylene)vinylacetate.

20. A stent according to claim **10** wherein the coating comprises a poly(hydroxy)ethylmethylmethacrylate.

21. A stent according to claim **10** wherein the coating comprises an acrylate based polymer.

22. A stent according to claim **10** wherein the coating comprises an acrylate based copolymer.

23. A stent according to claim **10** wherein the coating comprises a polyvinyl pyrrolidone.

24. A stent according to claim **10** wherein the coating comprises a cellulose ester.

25. A stent according to claim **10** wherein the coating comprises a fluorinated polymer.

26. A stent according to claim **10** wherein the fluorinated polymer is polytetrafluoroethylene.

27. A stent according to any one of claims **1** to **26** wherein said drug is a macrocyclic lactone analog of rapamycin.

28. A stent according to any one of claims **1** to **26** that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

29. A stent according to claim **28** wherein said drug is a macrocyclic lactone analog of rapamycin.

30. A stent according to any one of claims **1** to **26** that releases said rapamycin or macrocyclic lactone analog thereof over a period of at least 14 days.

31. A stent according to claim **30** wherein said drug is a macrocyclic lactone analog of rapamycin.

32. A stent according to any one of claims **1** to **26** wherein said rapamycin or macrocyclic lactone analog thereof is present in a therapeutically beneficial amount to inhibit neointimal proliferation.

33. A stent according to claim **32** wherein said drug is a macrocyclic lactone analog of rapamycin.

34. A stent according to claim 33 that releases said macrocyclic lactone analog of rapamycin over a period of at least 14 days.

35. A stent according to claim 34 wherein the coating comprises a fluorinated polymer.

36. A stent according to claim 35 wherein the coating further comprises an acrylate based polymer or copolymer.

37. A stent according to claim 33 that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

38. A stent according to claim 37 wherein the coating comprises a fluorinated polymer.

39. A stent according to claim 38 wherein the coating further comprises an acrylate based polymer or copolymer.

40. A device comprising a metallic stent, a biocompatible polymeric carrier and a drug, wherein said drug is rapamycin or a macrocyclic lactone analog thereof and is present in an amount effective to inhibit neointimal proliferation.

41. A device according to claim 40 wherein said polymeric carrier and drug are mixed together.

42. A device according to claim 40 wherein said polymeric carrier is bound to the drug.

43. A device according to claim 40 wherein the drug is entrapped on the surface of the stent by said polymeric carrier.

44. A device according to claim 40 wherein said stent comprises a generally thin walled cylinder containing a plurality of generally solid struts to which said polymeric carrier and drug are applied.

45. A device according to claim 44 further comprising a channel formed in at least one of said struts.

46. A device according to claim 45, wherein said channel has a closed perimeter on all sides, an open top and a generally rectangular perimeter, and said channel is smaller in all dimensions than said strut.

47. A device according to claim 40 wherein the polymeric carrier and drug are dip-coated onto the stent.

48. A device according to claim 40 wherein the polymeric carrier and drug are spray-coated onto the stent.

49. A device according to claim 40 wherein the weight ratio of drug to polymeric carrier is about 3:7.

50. A device according to claim 40 wherein the polymeric carrier comprises a degradable polymer.

51. A device according to claim 40 wherein the polymeric carrier comprises a nonabsorbable polymer.

52. A device according to claim 40 wherein the polymeric carrier comprises a lactone-based polyester; a lactone-based copolyester; a polyanhydride; a polyaminoacid; a polysaccharide; a polyphosphazene; a poly(ether-ester) copolymer; a polydimethylsiloxane; a poly(ethylene)vinylacetate; a poly (hydroxy)ethylmethylmethacrylate; an acrylate based polymer; an acrylate based copolymer; a polyvinyl pyrrolidone; a cellulose ester; a fluorinated polymer; or a blend thereof.

53. A device according to claim 52 wherein the polymeric carrier comprises a lactone-based polyester.

54. A device according to claim 52 wherein the polymeric carrier comprises a lactone-based copolyester.

55. A device according to claim 52 wherein the polymeric carrier comprises a polyanhydride.

56. A device according to claim 52 wherein the polymeric carrier comprises a polyaminoacid.

57. A device according to claim 52 wherein the polymeric carrier comprises a polysaccharide.

58. A device according to claim 52 wherein the polymeric carrier comprises a polyphosphazene.

59. A device according to claim 52 wherein the polymeric carrier comprises a poly(ether-ester) copolymer.

60. A device according to claim 52 wherein the polymeric carrier comprises a polydimethylsiloxane.

61. A device according to claim 52 wherein the polymeric carrier comprises a poly(ethylene)vinylacetate.

62. A device according to claim 52 wherein the polymeric carrier comprises a poly(hydroxy)ethylmethylmethacrylate.

63. A device according to claim 52 wherein the polymeric carrier comprises an acrylate based polymer.

64. A device according to claim 52 wherein the polymeric carrier comprises an acrylate based copolymer.

65. A device according to claim 52 wherein the polymeric carrier comprises a polyvinyl pyrrolidone.

66. A device according to claim 52 wherein the polymeric carrier comprises a cellulose ester.

67. A device according to claim 52 wherein the polymeric carrier comprises a fluorinated polymer.

68. A device according to claim 67 wherein the fluorinated polymer is polytetrafluoroethylene.

69. A device according to any one of claims 40 to 68 wherein said drug is a macrocyclic lactone analog of rapamycin.

70. A device according to any one of claims 40 to 68 that provides a controlled release of said rapamycin or macrocyclic lactone analog thereof over a period of several weeks.

71. A device according to claim 70 wherein said drug is a macrocyclic lactone analog of rapamycin.

72. A device according to claim 71 wherein the polymeric carrier comprises a fluorinated polymer.

73. A device according to claim 72 wherein the polymeric carrier further comprises an acrylate based polymer or copolymer.

74. A device according to any one of claims 40 to 68 that releases said drug over a period of at least 14 days.

75. A device according to claim 74 wherein said drug is a macrocyclic lactone analog of rapamycin.

76. A device according to claim 75 wherein the polymeric carrier comprises a fluorinated polymer.

77. A device according to claim 76 wherein the polymeric carrier further comprises an acrylate based polymer or copolymer.

* * * * *

EXHIBIT 3

US007229473B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,229,473 B2**
(45) **Date of Patent: *Jun. 12, 2007**

(54) **LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT**

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(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/466,983**

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(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 10/951,385, filed on Sep. 28, 2004, which is a continuation of application No. 10/408,328, filed on Apr. 7, 2003, now Pat. No. 6,808,536, which is a continuation of application No. 09/874,117, filed on Jun. 4, 2001, now Pat. No. 6,585,764, which is a continuation of application No. 09/061,586, filed on Apr. 16, 1998, now Pat. No. 6,273,913.

(60) Provisional application No. 60/044,692, filed on Apr. 18, 1997.

(51) **Int. Cl.**
A61F 2/06 (2006.01)

(52) **U.S. Cl.** **623/1.42**

(58) **Field of Classification Search** 623/1.42–1.48
See application file for complete search history.

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(57) **ABSTRACT**

Methods of preparing intravascular stents with a polymeric coating containing macrocyclic lactone (such as rapamycin or its analogs), stents and stent graphs with such coatings, and methods of treating a coronary artery with such devices. The macrocyclic lactone-based polymeric coating facilitates the performance of such devices in inhibiting restenosis.

5 Claims, 2 Drawing Sheets

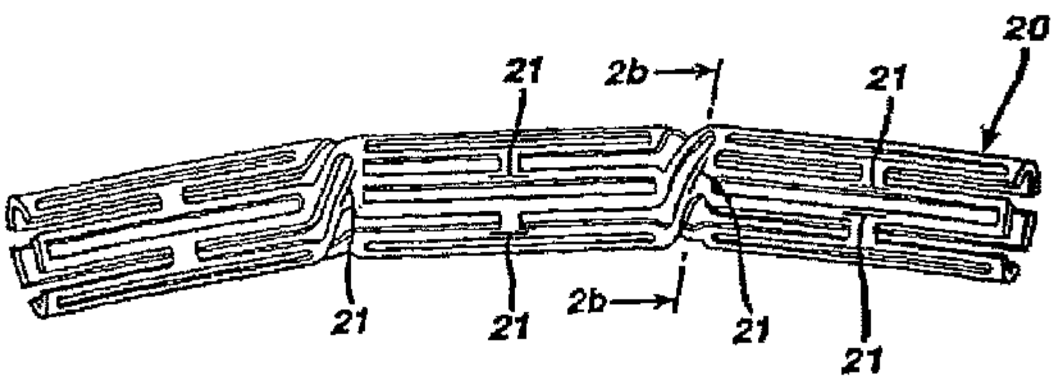

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FIG. 1

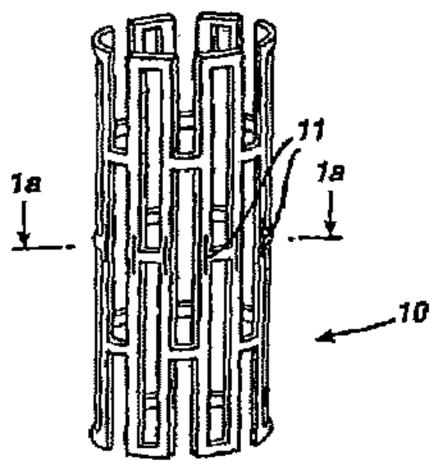


FIG. 1a

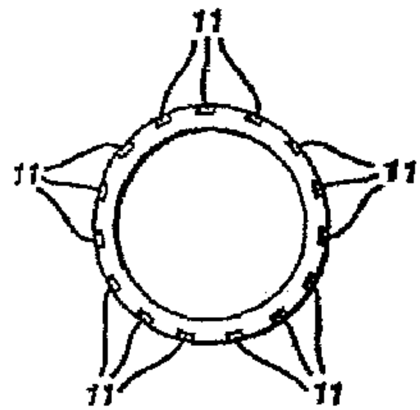


FIG. 2a

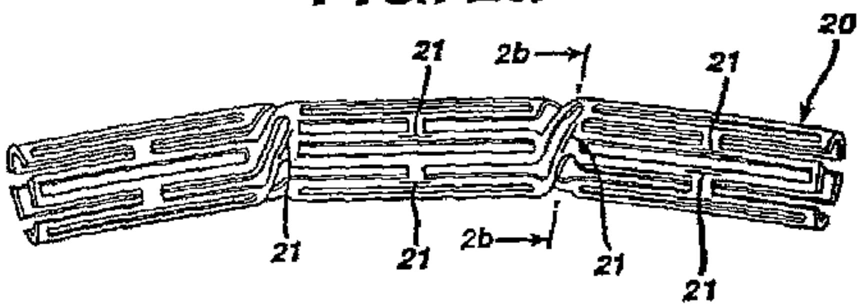


FIG. 2b

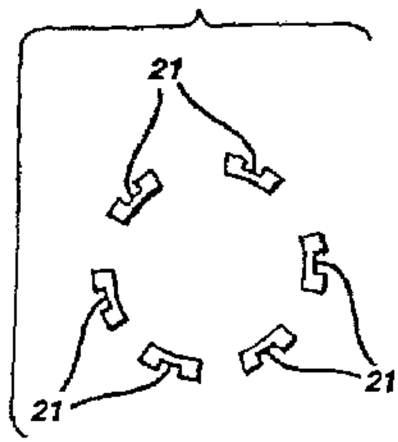


FIG. 3a

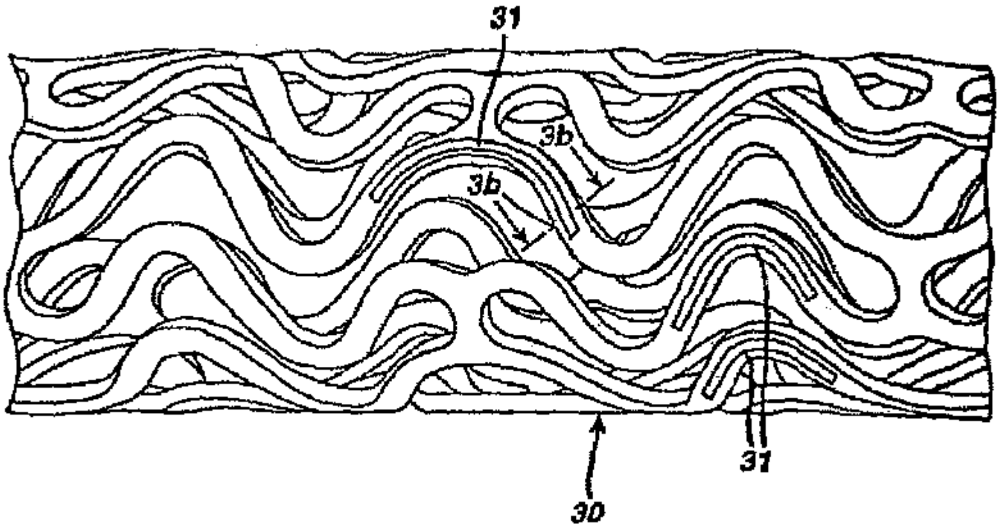


FIG. 3b

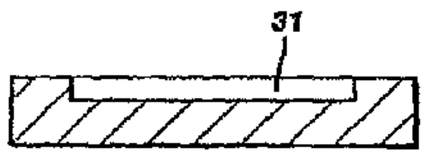
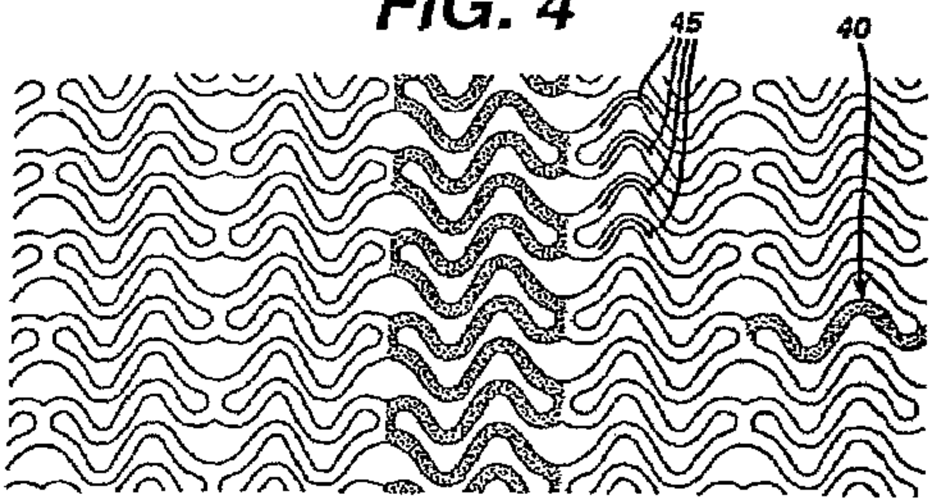


FIG. 4



LOCAL DELIVERY OF RAPAMYCIN FOR TREATMENT OF PROLIFERATIVE SEQUELAE ASSOCIATED WITH PTCA PROCEDURES, INCLUDING DELIVERY USING A MODIFIED STENT

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 10/951,385, filed Sep. 28, 2004, now pending, which is a continuation of Ser. No. 10/408,328, filed Apr. 7, 2003, now issued as U.S. Pat. No. 6,808,536, which is a continuation of application Ser. No. 09/874,117, filed Jun. 4, 2001, now issued as U.S. Pat. No. 6,585,764, which is a continuation of application Ser. No. 09/061,568, filed Apr. 16, 1998, now issued as U.S. Pat. No. 6,273,913, which in turn claims benefit of provisional application Ser. No. 60/044,692, filed Apr. 18, 1997. The disclosnres of these prior applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

Delivery of rapamycin locally, particularly from an intravascular stent, directly from micropores in the stent body or mixed or bound to a polymer coating applied on stent, to inhibit neointimal tissue proliferation and thereby prevent restenosis. This invention also facilitates the performance of the stent in inhibiting restenosis.

BACKGROUND OF THE INVENTION

Re-narrowing (restenosis) of an artherosclerotic coronary artery after percutaneous transluminal coronary angioplasty (PTCA) occurs in 10–50% of patients undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft. While the exact hormonal and cellular processes promoting restenosis are still being determined, our present nnderstanding is that the process of PTCA, besides opening the artherosclerotically obstructed artery, also injures resident coronary arterial smooth muscle cells (SMC). In response to this injury, adhering platelets, infiltrating macrophages, leukocytes, or the smooth mnscle cells (SMC) themselves release cell derived growth factors with subseqnent proliferation and migration of medial SMC through the internal elastic lamina to the area of the vessel intima. Further proliferation and hyperplasia of intimal SMC and, most significantly, production of large amounts of extracellular matrix over a period of 3–6 months results in the filling in and narrowing of the vascular space sufficient to significantly obstruct coronary blood flow.

Several recent experimental approaches to preventing SMC proliferation have shown promise althrough the mechanisms for most agents employed are still unclear. Heparin is the best known and characterized agent causing inhibition of SMC proliferation both in vitro and in animal models of balloon angioplasty-mediated injury. The mechanism of SMC inhibition with heparin is still not known bnt may be due to any or all of the following: 1) reduced expression of the growth regulatory protooncogenes c-fos and c-myc, 2) reduced cellnlar prodnction of tissne plnsminogen activator; are 3) binding and dequestration of growth regulatory factors such as fibrovalent growth factor (FGF).

Other agents which have demonstrated the ability to reduce myointimal thickening in animal models of balloon vascular injury are angiopeptin (a somatostatin analog), calcium channel blockers, angiotensin converting enzyme inhibitors (captopril, cilazapril), cyclosporin A, trapidil (an antianginal, antiplatelet agent), terbinafine (antifungal), colchicine and taxol (antitubulin antiproliferatives), and c-myc and c-myb antinsense oligonucleotides.

Additionally, a goat antibody to the SMC mitogen platelet derived growth factor (PDGF) has been shown to be effective in reducing myointimal thickening in a rat model of balloon angioplasty injury, thereby implicating PDGF directly in the etiology of restenosis. Thus, while no therapy has as yet proven successful clinically in preventing restenosis after angioplasty, the in vivo experimental success of several agents known to inhibit SMC growth suggests that these agents as a class have the capacity to prevent clinical restenosis and deserve careful evaluation in humans.

Coronary heart disease is the major cause of death in men over the age of 40 and in women over the age of fifty in the western world. Most coronary artery-related deaths are due to atherosclerosis. Atherosclerotic lesions which limit or obstruct coronary blood flow are the major cause of ischemic heart disease related mortality and result in 500,000–600,000 deaths in the United States annually. To arrest the disease process and prevent the more advanced disease states in which the cardiac muscle itself is compromised, direct intervention has been employed via percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) PTCA is a procedure in which a small balloon-tipped catheter is passed down a narrowed coronary artery and then expanded to re-open the artery. It is currently performed in approximately 250,000–300,000 patients each year. The major advantage of this therapy is that patients in which the procedure is successful need not undergo the more invasive surgical procednre of coronary artery bypass graft. A major difficulty with PTCA is the problem of post-angioplasty closure of the vessel, both immediately after PTCA (acute reocclusion) and in the long term (restenosis).

The mechanism of acnte reocclusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets along the damaged length of the newly opened blood vessel followed by formation of a fibrin/red blood cell thrombus. Recently, intravascular stents have been examined as a means of preventing acute reclosure after PTCA.

Restenosis (chronic reclosure) after angioplasty is a more gradual process than acute reocclusion: 30% of patients with subtotal lesions and 50% of patients with chronic total lesions will go on to restenosis after angioplasty. While the exact mechanism for restenosis is still under active investigation, the general aspects of the restenosis process have been identified.

In the normal arterial will, smooth muscle cells (SMC) proliferate at a low rate (<0.1%/day; ref). SMC in vessel wall exists in a contractile phenotype characterized by 80–90% of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, golgi bodies, and free ribosomes are few and located in the perinuclear region. Extracellular matrix surrounds SMC and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining SMC in the contractile phenotypic state.

Upon pressnre expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the arterial wall become injnred. Cell derived growth factors snch as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), etc. released from platelets (i.e., PDGF) adhering to the

damaged arterial luminal surface, invading macrophages and/or leukocytes, or directly from SMC (i.e., BFGF) provoke a proliferation and migratory response in medial SMC. These cells undergo a phenotypic change from the contractile phenotyope to a synthetic phenotype characterized by only few contractile filament bundles but extensive rough endoplasmic reticulum, golgi and free ribosomes. Proliferation/migration usually begins within 1–2 days post-injury and peaks at 2 days in the media, rapidly declining thereafter (Campbell et al., In: Vascular Smooth Muscle Cells in Culture, Campbell, J. H. and Campbell, G. R., Eds, CRC Press, Boca. Ratioh, 1987, pp. 39–55); Clowes, A. W. and Schwartz, S. M., Circ. Res. 56:139 145, 1985).

Finally, daughter synthetic cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate. Proliferation and migration continues until the damaged luminal endothelial layer regenerates at which time proliferation ceases within the intima, usually within 7–14 days postinjury. The remaining increase in intimal thickening which occurs over the next 3–6 months is due to an increase in extracellular matrix rather than cell number. Thus, SMC migration and proliferation is an acute response to vessel injury while intimal hyperplasia is a more chronic response. (Liu et al., Circulation, 79:1374–1387, 1989).

Patients with symptomatic reocclusion require either repeat PTCA or CABG. Because 30–50% of patients undergoing PTCA will experience restenosis, restenosis has clearly limited the success of PTCA as a therapeutic approach to coronary artery disease. Because SMC proliferation and migration are intimately involved with the pathophysiological response to arterial injury, prevention of SMC proliferation and migration represents a target for pharmacological intervention in the prevention of restenosis.

SUMMARY OF THE INVENTION

Novel Features and Applications to Stent Technology

Currently, attempts to improve the clinical performance of stents have involved some variation of either applying a coating to the metal, attaching a covering or membrane, or embedding material on the surface via ion bombardment. A stent designed to include reservoirs is a new approach which offers several important advantages over existing technologies.

Local Drug Delivery from a Stent to Inhibit Restenosis

In this application, it is desired to deliver a therapeutic agent to the site of arterial injury. The conventional approach has been to incorporate the therapeutic agent into a polymer material which is then coated on the stent. The ideal coating material must be able to adhere strongly to the metal stent both before and after expansion, be capable of retaining the drug at a sufficient load level to obtain the required dose, be able to release the drug in a controlled way over a period of several weeks, and be as thin as possible so as to minimize the increase in profile. In addition, the coating material should not contribute to any adverse response by the body (i.e., should be non-thrombogenic, non-inflammatory, etc.). To date, the ideal coating material has not been developed for this application.

An alternative would be to design the stent to contain reservoirs which could be loaded with the drug. A coating or membrane of biocompatable material could be applied over the reservoirs which would control the diffusion of the drug from the reservoirs to the artery wall.

One advantage of this system is that the properties of the coating can be optimized for achieving superior biocompatibility and adhesion properties, without the addition requirement of being able to load and release the drug. The size, shape, position, and number of reservoirs can be used to control the amount of drug, and therefore the dose delivered.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be better understood in connection with the following figures in which

FIGS. 1 and 1A are top views and section views of a stent containing reservoirs as described in the present invention;

FIGS. 2*a* and 2*b* are similar views of an alternate embodiment of the stent with open ends;

FIGS. 3*a* and 3*b* are further alternate figures of a device containing a grooved reservoir; and

FIG. 4 is a layout view of a device containing a reservoir as in FIG. 3.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Pharmacological attempts to prevent restenosis by pharmacologic means have thus far been unsuccessful and all involve systemic administration of the trial agents. Neither aspirin-dipyridamole, ticlopidine, acute heparin administration, chronic warfarin (6 months) nor methylprednisolone have been effective in preventing restenosis although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty. The calcium antagonists have also been unsuccessful in preventing restenosis, although they are still under study. Other agents currently under study include thromboxane inhibitors, prostacyclin mimetics, platelet membrane receptor blockers, thrombin inhibitors and angiotensin converting enzyme inhibitors. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; antiproliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Lang et al., 42 Ann. Rev. Med., 127–132 (1991); Popma et al., 84 Circulation, 1426–1436 (1991)).

Additional clinical trials in which the effectiveness for preventing restenosis of dietary fish oil supplements, thromboxane receptor antagonists, cholesterol lowering agents, and serotonin antagonists has been examined have shown either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Franklin, S. M. and Faxon, D. P., 4 Coronary Artery Disease, 2-32-242 (1993); Serruys, P. W. et al., 88 Circulation, (part 1) 1588–1601, (1993).

Conversely, stents have proven useful in preventing reducing the proliferation of restenosis. Stents, such as the stent 10 seen in layout in FIG. 4, balloon-expandable slotted metal tubes (usually but not limited to stainless steel), which when expanded within the lumen of an angioplastied coronary artery, provide structural support to the arterial wall. This support is helpful in maintaining an open path for blood flow. In two randomized clinical trials, stents were shown to increase angiographic success after PTCA, increase the stenosed blood vessel lumen and to reduce the lesion recurrence at 6 months (Serruys et al., 331 New Eng Jour. Med, 495, (1994); Fischman et al., 331 New Eng Jour. Med, 496–501 (1994). Additionally, in a preliminary trial, heparin coated stents appear to possess the same benefit of reduction in stenosis diameter at follow-up as was observed with non-heparin coated stents. Additionally, heparin coating appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et

al., 93 Circulation, 412–422, (1996). Thus, 1) sustained mechanical expansion of a stenosed coronary artery has been shown to provide some measure of restenosis prevention, and 2) coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs to local, injured tissue off the surface of the stent.

Numerous agents are being actively studied as antiproliferative agents for use in restenosis and have shown some activity in experimental animal models. These include: heparin aud heparin fragments (Clowes and Karnovsky, 265 Nature, 25-626, (1977); Guyton, J. R. et al. 46 Circ. Res., 625-634, (1980); Clowes, A. W. and Clowes, M. M., 52 Lab. Invest., 611-616, (1985); Clowes, A. W. and Clowes, M. M., 58 Circ. Res., 839–845 (1986); Majesky et al., 61 Circ Res., 296-300, (1987); Snow et al., 137 Am. J. Pathol., 313–330 (1990); Okada, T. et al., 25 Neurosurgery, 92–898, (1989) colchicine (Currier, J. W. et al., 80 Circulation, 11–66, (1989), taxol (ref), agiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., 245 Science, 186–188 (1989), angiopeptin (Lundergan, C. F. et al., 17 Am. J. Cardiol. (Suppl. B); 132B-136B (1991), Cyclosporin A (Jonasson, L. et. al., 85 Proc. Natl, Acad. Sci., 2303 (1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., 253 Science, 1129–1132 (1991), terbinafine (Nemecek, G. M. et al., 248 J. Pharmacol. Exp. Thera., 1167-11747 (1989), trapidil (Lin, M. W. et al., 81 Circulation, 1089-1093 (1990), interferon-gamma (Hansson, G. K. and Holm, 84 J. Circulation, 1266–1272 (1991), steroids (Colburn, M. D. et al., 15 J. Vasc. Surg., 510–518 (1992), see also Berk, B. C. et al., 17 J. Am. Coll. Cardiol., 111B–117B (1991), ionizing radiation (ref), fusion toxins (ref) antisense oligonucleotides (ref), gene vectors (ref), and rapamycin (see below).

Of particular interest in rapamycin. Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses antiinflammatory activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G.sub.1 to 5 phase progression of T-cells through the cell cycle by inhibiting specific cell cyclins and cyclin-dependent protein kinases (Siekierka, Immunol. Res. 13: 110–116, 1994). The antiproliferative action of rapamycin is not limited to T-cells; Mark et al. (Circ Res 76:412-417, 1995) have demonstrated that rapamycin prevents proliferation of both rat and human SMC in vitro while Poon et al. have shown the rat, porcine, and human SMC migratin can also be inhibited by rapamycin (J Clin Invest 98: 2277–2283, 1996). Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. In fact, the combined effects of rapamycin have been demonstrated to result in a diminished SMC hyperproliferative response in a rat femoral artery graft model and in both rat and porcine arterial balloon injury models (Gregory et al., Transplantation 55:1409–1418, 1993; Gallo et al., in press, (1997)). These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

Although the ideal agent for restenosis has not yet been identified, some desired properties are clear: inhibition of local thrombosis without the risk systemic bleeding complications and continuous and prevention of the dequale of arterial injury, including local inflammation and sustained prevention smooth muscle proliferation at the site of angioplasty without serious systemic complications. Inasmuch as stents prevent at least a portion of the restenosis process, an agent which prevents inflammation and the proliferation of SMC combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

Experiments

Agents: Rapamycin (sirolimus) structural analogs (macrocyclic lactones) and inhibitors of cell-cycle progression.

Delivery Methods: These can vary:

Local delivery of such agents (rapamycin) from the struts of a stent, from a stent graft, grafts, stent cover or sheath.

Involving comixture with polymers (both degradable and nondegrading) to hold the drug to the stent or graft.

or entrapping the drug into the metal of the stent or graft body which has been modified to contain micropores or channels, as will be explained further herein.

or including covalent binding of the drug to the stent via solution chemistry techniques (such as via the Carmeda process) or dry chemistry techniques (e.g. vapour deposition methods such as rf-plasma polymerization) and combinations thereof.

Catheter delivery intravascularly from a tandem balloon or a porous balloon for intramural uptake.

Extravascular delivery by the pericardial route.

Extravascular delivery by the advential application of sustained release formulations.

Uses:

for inhibition of cell proliferation to prevent neointimal proliferation and restenosis.

prevention of tumor expansion from stents.

prevent ingrowth of tissue into catheters and shunts inducing their failure.

1. Experimental Stent Delivery Method—Delivery from Polymer Matrix:

Solution of Rapamycin, prepared in a solvent miscible with polymer carrier solution, is mixed with solution of polymer at final concentration range 0.001 weight % to 30 weight % of drug. Polymers are biocompatible (i.e., not elicit any negative tissue reaction or promote mural thrombus formation) and degradable, such as lactone-based polyesters or copolyesters, e.g., polylactide, polycaprolactonglycolide, polyorthoesters, polyanhydrides; poly-amino acids; polysaccharides; polyphosphazenes; poly(ether-ester) copolymers, e.g., PEO-PLLA, or blends thereof. Nonabsorbable biocompatible polymers are also suitable candidates. Polymers such as polydimethylsiolxane; poly(ethylene-vingylacetate); acrylate based polymers or copolymers, e.g., poly(hydroxyethyl methylmethacrylate, polyvinyl pyrrolidinone; fluorinated polymers such as polytetrafluoroethylene; cellulose esters.

Polymer/drug mixture is applied to the surfaces of the stent by either dip-coating, or spray coating, or brush coating or dip/spin coating or combinations thereof, and the solvent allowed to evaporate to leave a film with entrapped rapamycin.

2. Experimental Stent Delivery Method—Delivery from Microporous Depots in Stent Through a Polymer Membrane Coating:

Stent, whose body has been modified to contain micropores or channels is dipped into a solution of Rapamycin, range 0.001 wt % to saturated, in organic solvent such as acetone or methylene chloride, for sufficient time to allow solution to permeate into the pores. (The dipping solution can also be compressed to improve the loading efficiency.) After solvent has been allowed to evaporate, the stent is dipped briefly in fresh solvent to remove excess surface bound drug. A solution of polymer, chosen from any

identified in the first experimental method, is applied to the stent as detailed above. This outer layer of polymer will act as diffusion-controller for release of drug.

3. Experimental Stent Delivery Method—Delivery via Lysis of a Covalent Drug Tether:

Rapamycin is modified to contain a hydrolytically or enzymatically labile covalent bond for attaching to the surface of the stent which itself has been chemically derivatized to allow covalent immobilization. Covalent bonds such as ester, amides or anhydrides may be suitable for this.

4. Experimental Method—Pericardial Delivery:

A: Polymeric Sheet

Rapamycin is combined at concentration range previously highlighted, with a degradable polymer such as poly(caprolactone-gylcolid-e) or non-degradable polymer, e.g., polydimethylsiloxane, and mixture cast as a thin sheet, thickness range 10.mu. to 1000.mu. The resulting sheet can be wrapped perivascularly on the target vessel. Preference would be for the absorbable polymer.

B: Conformal Coating:

Rapamycin is combined with a polymer that has a melting temperature just above 37° C., range 40°–45° C. Mixture is applied in a molten state to the external side of the target vessel. Upon cooling to body temperature the mixture solidifies conformably to the vessel wall. Both non-degradable and absorbable biocompatible polymers are suitable.

As seen in the figures it is also possible to modify currently manufactured stents in order to adequately provide the drug dosages such as rapamycin. As seen in FIGS. **1***a*, **2***a* and **3***a*, any stent strut **10**, **20**, **30** can be modified to have a certain reservoir or channel **11**, **21**, **31**. Each of these reservoirs can be open or closed as desired. These reservoirs can hold the drug to be delivered. FIG. **4** shows a stent **40** with a reservoir **45** created at the apex of a flexible strut. Of course, this reservoir **45** is intended to be useful to deliver rapamycin or any other drug at a specific point of flexibility of the stent. Accordingly, this concept can be useful for "second generation" type stents.

In any of the foregoing devices, however, it is useful to have the drug dosage applied with enough specificity and enough concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the stent struts must be kept at a size of about 0.0005" to about 0.003". Then, it should be possible to adequately apply the drug dosage at the desired location and in the desired amount.

These and other concepts will are disclosed herein. It would be apparent to the reader that modifications are possible to the stent or the drug dosage applied. In any event, however, the any obvious modifications should be perceived to fall within the scope of the invention which is to be realized from the attached claims and their equivalents.

What is claimed:

1. A metallic stent having a coating applied thereto, wherein:
 - said coating comprises a mixture of a biocompatible polymeric carrier and a therapeutic agent;
 - said polymeric carrier comprises at least one nonabsorbable polymer;
 - said therapeutic agent is rapamycin, or a macrocyclic lactone analog thereof, present in an amount effective to inhibit neointimal proliferation; and
 - said stent provides a controlled release of said therapeutic agent over a period of several weeks.

2. The metallic stent according to claim **1** wherein said therapeutic agent is a macrocyclic lactone analog of rapamycin.

3. The metallic stent according to claim **1** wherein said biocompatible polymeric carrier comprises a fluorinated polymer.

4. The metallic according to claim **3** wherein said biocompatible polymeric carrier further comprises an acrylate-based polymer or copolymer.

5. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting a metallic stent according to any one of claims **1** to **4** in the lumen of said coronary artery.

* * * * *

EXHIBIT 4

US007300662B2

(12) **United States Patent**
Falotico et al.

(10) **Patent No.: US 7,300,662 B2**
(45) **Date of Patent: *Nov. 27, 2007**

(54) **DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE**

(75) Inventors: **Robert Falotico**, Belle Mead, NJ (US); **Gregory A. Kopia**, Hillsborough, NJ (US); **Gerard H. Llanos**, Stewartsville, NJ (US)

(73) Assignee: **Cordis Corporation**, Miami Lakes, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 503 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/829,074**

(22) Filed: **Apr. 21, 2004**

(65) **Prior Publication Data**

US 2004/0260268 A1 Dec. 23, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/850,293, filed on May 7, 2001, now abandoned, which is a continuation-in-part of application No. 09/575,480, filed on May 19, 2000.

(60) Provisional application No. 60/263,979, filed on Jan. 25, 2001, provisional application No. 60/263,806, filed on Jan. 24, 2001, provisional application No. 60/262,614, filed on Jan. 18, 2001, provisional application No. 60/262,461, filed on Jan. 18, 2001, provisional application No. 60/204,417, filed on May 12, 2000.

(51) **Int. Cl.**
A61F 2/00 (2006.01)
A61F 2/06 (2006.01)

(52) **U.S. Cl.** 424/424; 623/1.42; 623/1.45

(58) **Field of Classification Search** 424/422–426; 623/1.42–1.48
See application file for complete search history.

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(57) **ABSTRACT**

A drug and drug delivery system may be utilized in the treatment of vascular disease. A local delivery system is coated with rapamycin or other suitable drug, agent or compound and delivered intraluminally for the treatment and prevention of neointimal hyperplasia following percutaneons transluminal coronary angiography. The local delivery of the drugs or agents provides for increased effectiveness and lower systemic toxicity.

25 Claims, 2 Drawing Sheets

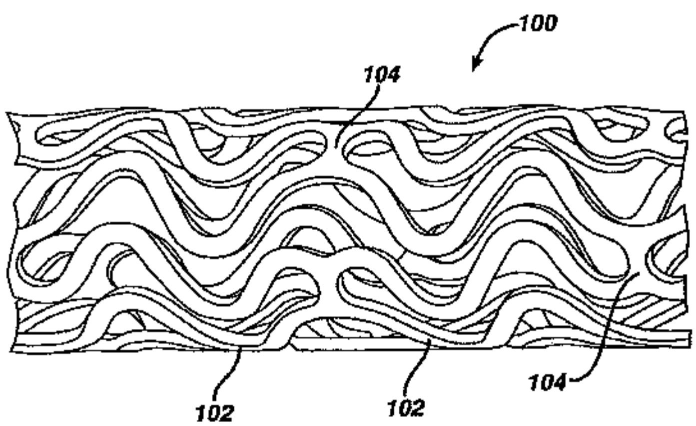

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FIG. 1

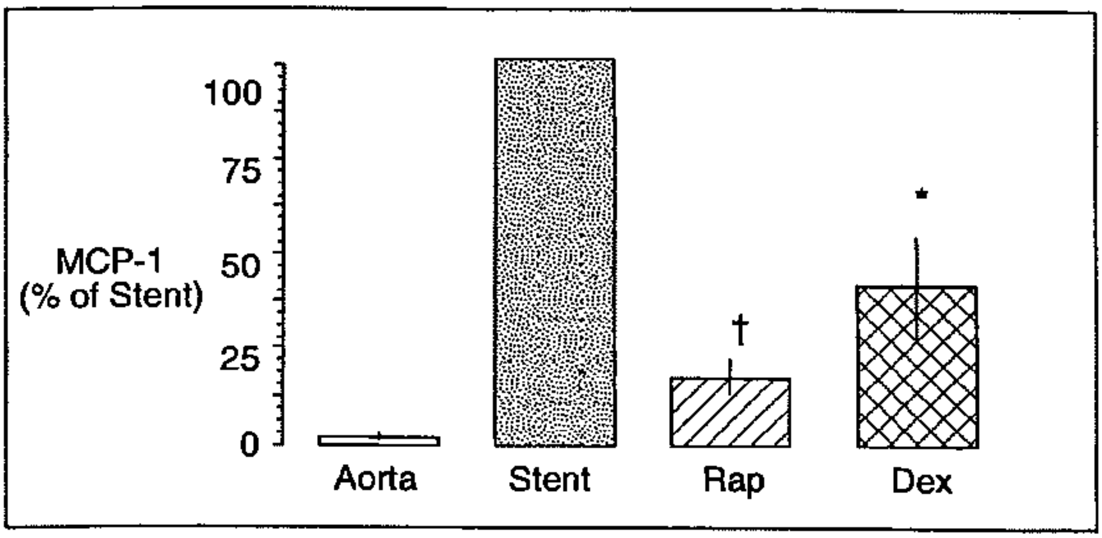


FIG. 2

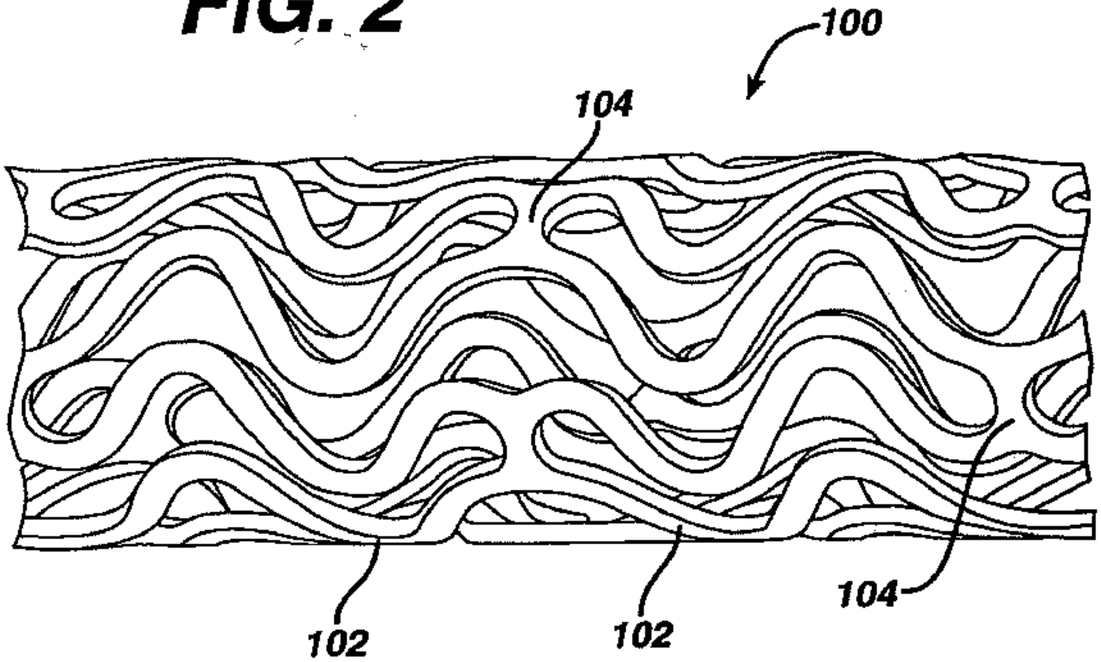
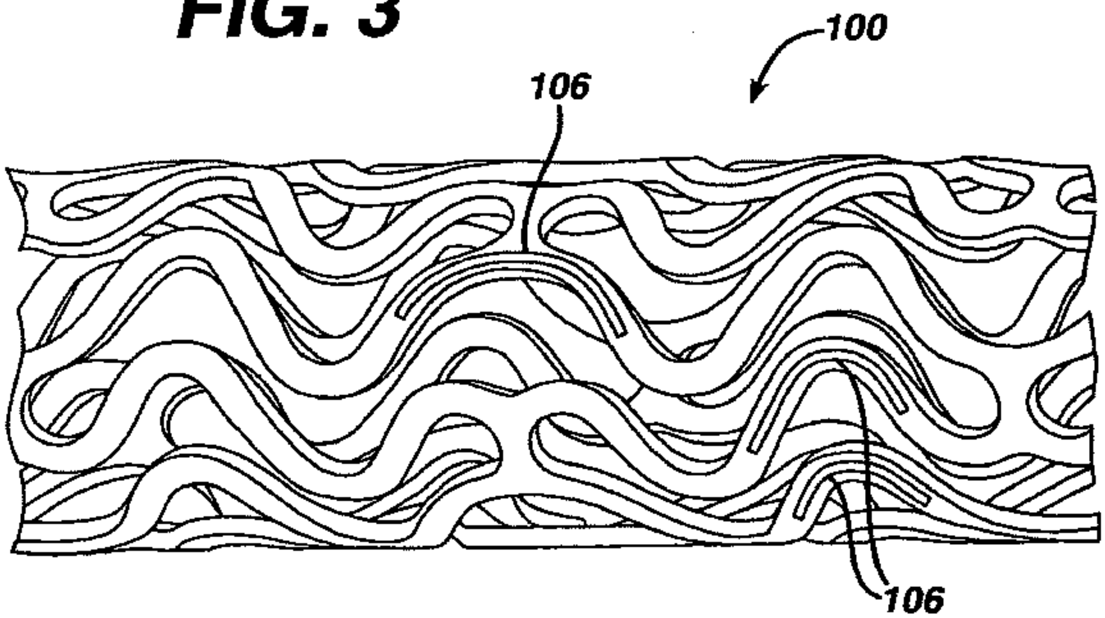


FIG. 3



DRUG/DRUG DELIVERY SYSTEMS FOR THE PREVENTION AND TREATMENT OF VASCULAR DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 09/850,293, filed May 7, 2001, now abandoned, which in turn claims priority of U.S. Provisional Application No. 60/263,979, filed Jan. 25, 2001, U.S. Provisional Application No. 60/263,806, filed January 24, 2001, U.S. Provisional Application No. 60/262,614, filed Jan. 18, 2001, U.S. Provisional Application No. 60/262,461, filed Jan. 18, 2001, and is a continuation-in-part of U.S. Application No. 09,575,480, filed May 19, 2000, now pending, which in turn claims priority of U.S. Provisional Application No. 60/204,4 17, filed May 12, 2000.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to drugs and drug delivery systems for the prevention and treatment of vascular disease, and more particularly to drugs and drug delivery systems for the prevention and treatment of neointimal hyperplasia.

2. Discussion of the Related Art

Many individuals suffer from circulatory disease caused by a progressive blockage of the blood vessels that perfuse the heart and other major organs with nutrients. More severe blockage of blood vessels in such individuals often leads to hypertension, ischemic injury, stroke, or myocardial infarction. Atherosclerotic lesions, which limit or obstruct coronary blood flow, are the major cause of ischemic heart disease. Percutaneous transluminal coronary angioplasty is a medical procedure whose purpose is to increase blood flow through an artery. Percutaneous transluminal coronary angioplasty is the predominant treatment for coronary vessel stenosis. The increasing use of this procedure is attributable to its relatively high success rate and its minimal invasiveness compared with coronary bypass surgery. A limitation associated with percutaneous transluminal coronary angioplasty is the abrupt closure of the vessel which may occur immediately after the procedure and restenosis which occurs gradually following the procedure. Additionally, restenosis is a chronic problem in patients who have undergone saphenous vein bypass grafting. The mechanism of acute occlusion appears to involve several factors and may result from vascular recoil with resultant closure of the artery and/or deposition of blood platelets and fibrin along the damaged length of the newly opened blood vessel.

Restenosis after percutaneous transluminal coronary angioplasty is a more gradual process initiated by vascular injury. Multiple processes, including thrombosis, inflammation, growth factor and cytokine release, cell proliferation, cell migration and extracellular matrix synthesis each contribute to the restenotic process.

While the exact mechanism of restenosis is not completely understood, the general aspects of the restenosis process have been identified. In the normal arterial wall, smooth muscle cells proliferate at a low rate, approximately less than 0.1 percent per day. Smooth muscle cells in the vessel walls exist in a contractile phenotype characterized by eighty to ninety percent of the cell cytoplasmic volume occupied with the contractile apparatus. Endoplasmic reticulum, Golgi, and free ribosomes are few and are located in the perinuclear region. Extracellular matrix surrounds the

smooth muscle cells and is rich in heparin-like glycosylaminoglycans which are believed to be responsible for maintaining smooth muscle cells in the contractile phenotypic state (Campbell and Campbell, 1985).

Upon pressure expansion of an intracoronary balloon catheter during angioplasty, smooth muscle cells within the vessel wall become injured, initiating a thrombotic and inflammatory response. Cell derived growth factors such as platelet derived growth factor, fibroblast growth factor, epidermal growth factor, thrombin, etc., released from platelets, invading macrophages and/or leukocytes, or directly from the smooth muscle cells provoke proliferative and migratory responses in medial smooth muscle cells. These cells undergo a change from the contractile phenotype to a synthetic phenotype characterized by only a few contractile filament bundles, extensive rough endoplasmic reticulum, Golgi and free ribosomes. Proliferation/migration usually begins within one to two days post-injury and peaks several days thereafter (Campbell and Campbell, 1987; Clowes and Schwartz, 1985).

Daughter cells migrate to the intimal layer of arterial smooth muscle and continue to proliferate and secrete significant amounts of extracellular matrix proteins. Proliferation, migration and extracellular matrix synthesis continue until the damaged endothelial layer is repaired at which time proliferation slows within the intima, usually within seven to fourteen days post-injury. The newly formed tissue is called neointima. The further vascular narrowing that occurs over the next three to six months is due primarily to negative or constrictive remodeling.

Simultaneous with local proliferation and migration, inflammatory cells invade the site of vascular injury. Within three to seven days post-injury, inflammatory cells have migrated to the deeper layers of the vessel wall. In animal models employing either balloon injury or stent implantation, inflammatory cells may persist at the site of vascular injury for at least thirty days (Tanaka et al., 1993; Edelman et al., 1998). Inflammatory cells therefore are present and may contribute to both the acute and chronic phases of restenosis.

Numerous agents have been examined for presumed anti-proliferative actions in restenosis and have shown some activity in experimental animal models. Some of the agents which have been shown to successfully reduce the extent of intimal hyperplasia in animal models include: heparin and heparin fragments (Clowes, A. W. and Karnovsky M., Nature 265: 25-26, 1977; Guyton, J. R. et al., Circ. Res., 46: 625-634, 1980; Clowes, A. W. and Clowes, M. M., Lab. Invest. 52: 611-616, 1985; Clowes, A. W. and Clowes, M. M., Circ. Res. 58: 839-845, 1986; Majesky et al., Circ. Res. 61: 296-300, 1987; Snow et al., Am. J. Pathol. 137: 313-330, 1990; Okada, T. et al., Neurosurgery 25: 92-98, 1989), colchicine (Currier, J. W. et al., Circ. 80: 11-66, 1989), taxol (Sollot, S. J. et al., J. Clin. Invest. 95: 1869-1876, 1995), angiotensin converting enzyme (ACE) inhibitors (Powell, J. S. et al., Science, 245: 186-188, 1989), angiopeptin (Lundergan, C. F. et al. Am. J. Cardiol. 17(Suppl. B):132B-136B, 1991), cyclosporin A (Jonasson, L. et al., Proc. Natl., Acad. Sci., 85: 2303, 1988), goat-anti-rabbit PDGF antibody (Ferns, G. A. A., et al., Science 253: 1129-1132, 1991), terbinafine (Nemecek, G. M. et al., J. Pharmacol. Exp. Thera. 248: 1167-1174, 1989), trapidil (Liu, M. W. et al., Circ. 81: 1089-1093, 1990), tranilast (Fukuyama, J. et al., Eur. J. Pharmacol. 318: 327-332, 1996), interferon-gamma (Hansson, G. K. and Holm, J., Circ. 84: 1266-1272, 1991), rapamycin (Marx, S. O. et al., Circ. Res. 76: 412-417, 1995), corticosteroids (Colburn, M. D. et al., J. Vasc. Surg. 15:

510-518, 1992), see also Berk, B. C. et al., J. Am. Coll. Cardiol. 17: 111B-117B, 1991), ionizing radiation (Weinberger, J. et al., Int. J. Rad. Onc. Biol. Phys. 36: 767-775, 1996), fusion toxins (Farb, A. et al., Circ. Res. 80: 542-550, 1997) antisense oligonucleotides (Simons, M. et al., Nature 359: 67-70, 1992) and gene vectors (Chang, M. W. et al., J. Clin. Invest. 96: 2260-2268, 1995). Anti-proliferative effects on smooth muscle cells in vitro have been demonstrated for many of these agents, including heparin and heparin conjugates, taxol, tranilast, colchicine, ACE inhibitors, fusion toxins, antisense oligonucleotides, rapamycin and ionizing radiation. Thus, agents with diverse mechanisms of smooth muscle cell inhibition may have therapeutic utility in reducing intimal hyperplasia.

However, in contrast to animal models, attempts in human angioplasty patients to prevent restenosis by systemic pharmacologic means have thus far been unsuccessful. Neither aspirin-dipyridamole, ticlopidine, anti-coagulant therapy (acute heparin, chronic warfarin, hirudin or hirulog), thromboxane receptor antagonism nor steroids have been effective in preventing restenosis, although platelet inhibitors have been effective in preventing acute reocclusion after angioplasty (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991). The platelet GP IIb/IIIa receptor, antagonist, Reopro is still under study but has not shown promising results for the reduction in restenosis following angioplasty and stenting. Other agents, which have also been unsuccessful in the prevention of restenosis, include the calcium channel antagonists, prostacyclin mimetics, angiotensin converting enzyme inhibitors, serotonin receptor antagonists, and anti-proliferative agents. These agents must be given systemically, however, and attainment of a therapeutically effective dose may not be possible; anti-proliferative (or anti-restenosis) concentrations may exceed the known toxic concentrations of these agents so that levels sufficient to produce smooth muscle inhibition may not be reached (Mak and Topol, 1997; Lang et al., 1991; Popma et al., 1991).

Additional clinical trials in which the effectiveness for preventing restenosis utilizing dietary fish oil supplements or cholesterol lowering agents has been examined showing either conflicting or negative results so that no pharmacological agents are as yet clinically available to prevent post-angioplasty restenosis (Mak and Topol, 1997; Franklin and Faxon, 1993: Serruys, P. W. et al., 1993). Recent observations suggest that the antilipid/antioxidant agent, probucol may be useful in preventing restenosis but this work requires confirmation (Tardif et al., 1997; Yokoi, et al., 1997). Probucol is presently not approved for use in the United States and a thirty-day pretreatment period would preclude its use in emergency angioplasty. Additionally, the application of ionizing radiation has shown significant promise in reducing or preventing restenosis after angioplasty in patients with stents (Teirstein et al., 1997). Currently, however, the most effective treatments for restenosis are repeat angioplasty, atherectomy or coronary artery bypass grafting, because no therapeutic agents currently have Food and Drug Administration approval for use for the prevention of post-angioplasty restenosis.

Unlike systemic pharmacologic therapy, stents have proven effective in significantly reducing restenosis. Typically, stents are balloon-expandable slotted metal tubes (usually, but not limited to, stainless steel), which, when expanded within the lumen of an angioplastied coronary artery, provide structural support through rigid scaffolding to the arterial wall. This support is helpful in maintaining vessel lumen patency. In two randomized clinical trials, stents increased angiographic success after percutaneous transluminal coronary angioplasty, by increasing minimal lumen diameter and reducing, but not eliminating, the incidence of restenosis at six months (Serruys et al., 1994; Fischman et al., 1994).

Additionally, the heparin coating of stents appears to have the added benefit of producing a reduction in sub-acute thrombosis after stent implantation (Serruys et al., 1996). Thus, sustained mechanical expansion of a stenosed coronary artery with a stent has been shown to provide some measure of restenosis prevention, and the coating of stents with heparin has demonstrated both the feasibility and the clinical usefulness of delivering drugs locally, at the site of injured tissue.

Accordingly, there exists a need for effective drugs and drug delivery systems for the effective prevention and treatment of neointimal thickening that occurs after percutaneous transluminal coronary angioplasty and stent implantation.

SUMMARY OF THE INVENTION

The drugs and drug delivery systems of the present invention provide a means for overcoming the difficulties associated with the methods and devices currently in use as briefly described above.

In accordance with one aspect, the present invention is directed to a method for the prevention of constrictive remodeling. The method comprises the controlled delivery, by release from an intraluminal medical device, of a compound in therapeutic dosage amounts.

In accordance with another aspect, the present invention is directed to a drug delivery device. The drug delivery device comprises an intraluminal medical device and a therapeutic dosage of an agent releasably affixed to the intraluminal medical device for the treatment of constrictive vascular remodeling.

The drugs and drug delivery systems of the present invention utilize a stent or graft in combination with rapamycin or other drugs/agents/compounds to prevent and treat neointimal hyperplasia, i.e. restenosis, following percutaneous transluminal coronary angioplasty and stent implantation. It has been determined that rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. It has also been determined that rapamycin eluting stent coatings produce superior effects in humans, when compared to animals, with respect to the magnitude and duration of the reduction in neointimal hyperplasia. Rapamycin administration from a local delivery platform also produces an anti-inflammatory effect in the vessel wall that is distinct from and complimentary to its smooth muscle cell anti-proliferative effect. In addition, it has also been demonstrated that rapamycin inhibits constrictive vascular remodeling in humans.

Other drugs, agents or compounds which mimic certain actions of rapamycin may also be utilized in combination with local delivery systems or platforms.

The local administration of drugs, agents or compounds to stented vessels have the additional therapeutic benefit of higher tissue concentration than that which would be achievable through the systemic administration of the same drugs, agents or compounds. Other benefits include reduced systemic toxicity, single treatment, and ease of administration. An additional benefit of a local delivery device and drug, agent or compound therapy may be to reduce the dose of the therapeutic drugs, agents or compounds and thus limit their toxicity, while still achieving a reduction in restenosis.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other features and advantages of the invention will be apparent from the following, more particular description of preferred embodiments of the invention, as illustrated in the accompanying drawings.

FIG. 1 is a chart indicating the effectiveness of rapamycin as an anti-inflammatory relative to other anti-inflammatories.

FIG. 2 is a view along the length of a stent (ends not shown) prior to expansion showing the exterior surface of the stent and the characteristic banding pattern.

FIG. 3 is a perspective view of the stent of FIG. 1 having reservoirs in accordance with the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As stated above, the proliferation of vascular smooth muscle cells in response to mitogenic stimuli that are released during balloon angioplasty and stent implantation is the primary cause of neointimal hyperplasia. Excessive neointimal hyperplasia can often lead to impairment of blood flow, cardiac ischemia and the need for a repeat intervention in selected patients in high risk treatment groups. Yet repeat revascularization incurs risk of patient morbidity and mortality while adding significantly to the cost of health care. Given the widespread use of stents in interventional practice, there is a clear need for safe and effective inhibitors of neointimal hyperplasia.

Rapamycin is a macroyclic triene antibiotic produced by streptomyces hygroscopicus as disclosed in U.S. Pat. No. 3,929,992. It has been found that rapamycin inhibits the proliferation of vascular smooth muscle cells in vivo. Accordingly, rapamycin may be utilized in treating intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion in a mammal, particularly following either biologically or mechanically mediated vascular injury, or under conditions that would predispose a mammal to suffering such a vascular injury. Rapamycin functions to inhibit smooth muscle cell proliferation and does not interfere with the re-endothelialization of the vessel walls.

Rapamycin functions to inhibit smooth muscle cell proliferation through a number of mechanisms. In addition, rapamycin reduces the other effects caused by vascular injury, for example, inflammation. The operation and various functions of rapamycin are described in detail below. Rapamycin as used throughout this application shall include rapamycin, rapamycin analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

Rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty. Inhibition of growth factor and cytokine mediated smooth muscle proliferation at the late G1 phase of the cell cycle is believed to be the dominant mechanism of action of rapamycin. However, rapamycin is also known to prevent T-cell proliferation and differentiation when administered systemically. This is the basis for its immunosuppresive activity and its ability to prevent graft rejection.

The molecular events that are responsible for the actions of rapamycin, a known anti-proliferative, which acts to reduce the magnitude and duration of neointimal hyperplasia, are still being elucidated. It is known, however, that rapamycin enters cells and binds to a high-affinity cytosolic protein called FKBP12. The complex of rapamycin and FKPB12 in turn binds to and inhibits a phosphoinositide (PI)-3 kinase called the "mammalian Target of Rapamycin" or TOR. TOR is a protein kinase that plays a key role in mediating the downstream signaling events associated with mitogenic growth factors and cytokines in smooth muscle cells and T lymphocytes. These events include phosphorylation of p27, phosphorylation of p70 s6 kinase and phosphorylation of 4BP-1, an important regulator of protein translation.

It is recognized that rapamycin reduces restenosis by inhibiting neointimal hyperplasia. However, there is evidence that rapamycin may also inhibit the other major component of restenosis, namely, negative remodeling. Remodeling is a process whose mechanism is not clearly understood but which results in shrinkage of the external elastic lamina and reduction in lumenal area over time, generally a period of approximately three to six months in humans.

Negative or constrictive vascular remodeling may be quantified angiographically as the percent diameter stenosis at the lesion site where there is no stent to obstruct the process. If late lumen loss is abolished in-lesion, it may be inferred that negative remodeling has been inhibited. Another method of determining the degree of remodeling involves measuring in-lesion external elastic lamina area using intravascular ultrasound (IVUS). Intravascular ultrasound is a technique that can image the external elastic lamina as well as the vascular lumen. Changes in the external elastic lamina proximal and distal to the stent from the post-procedural timepoint to four-month and twelve-month follow-ups are reflective of remodeling changes.

Evidence that rapamycin exerts an effect on remodeling comes from human implant studies with rapamycin coated stents showing a very low degree of restenosis in-lesion as well as in-stent. In-lesion parameters are usually measured approximately five millimeters on either side of the stent i.e. proximal and distal. Since the stent is not present to control remodeling in these zones which are still affected by balloon expansion, it may be inferred that rapamycin is preventing vascular remodeling.

The data in Table 1 below illustrate that in-lesion percent diameter stenosis remains low in the rapamycin treated groups, even at twelve months. Accordingly, these results support the hypothesis that rapamycin reduces remodeling.

TABLE 1.0

Angiographic In-Lesion Percent Diameter Stenosis (%, mean ± SD and "n=") In Patients Who Received a Rapamycin-Coated Stent

Coating Group	Post Placement	4–6 month Follow Up	12 month Follow Up
Brazil	10.6 ± 5.7 (30)	13.6 ± 8.6 (30)	22.3 ± 7.2 (15)
Netherlands	14.7 ± 8.8	22.4 ± 6.4	—

Additional evidence supporting a reduction in negative remodeling with rapamycin comes from intravascular ultrasound data that was obtained from a first-in-man clinical program as illustrated in Table 2 below.

TABLE 2.0

Matched IVUS data in Patients Who Received a Rapamycin-Coated Stent

IVUS Parameter	Post (n=)	4-Month Follow-Up (n=)	12-Month Follow-Up (n=)
Mean proximal vessel area (mm^2)	16.53 ± 3.53 (27)	16.31 ± 4.36 (28)	13.96 ± 2.26 (13)
Mean distal vessel area (mm^2)	13.12 ± 3.68 (26)	13.53 ± 4.17 (26)	12.49 ± 3.25 (14)

The data illustrated that there is minimal loss of vessel area proximally or distally which indicates that inhibition of negative remodeling has occurred in vessels treated with rapamycin-coated stents.

Other than the stent itself, there have been no effective solutions to the problem of vascular remodeling. Accordingly, rapamycin may represent a biological approach to controlling the vascular remodeling phenomenon.

It may be hypothesized that rapamycin acts to reduce negative remodeling in several ways. By specifically blocking the proliferation of fibroblasts in the vascular wall in response to injury, rapamycin may reduce the formation of vascular scar tissue. Rapamycin may also affect the translation of key proteins involved in collagen formation or metabolism.

Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

In a preferred embodiment, the rapamycin is delivered by a local delivery device to control negative remodeling of an arterial segment after balloon angioplasty as a means of reducing or preventing restenosis. While any delivery device may be utilized, it is preferred that the delivery device comprises a stent that includes a coating or sheath which elutes or releases rapamycin. The delivery system for such a device may comprise a local infusion catheter that delivers rapamycin at a rate controlled by the administrator.

Rapamycin may also be delivered systemically using an oral dosage form or a chronic injectible depot form or a patch to deliver rapamycin for a period ranging from about seven to forty-five days to achieve vascular tissue levels that are sufficient to inhibit negative remodeling. Such treatment is to be used to reduce or prevent restenosis when administered several days prior to elective angioplasty with or without a stent.

Data generated in porcine and rabbit models show that the release of rapamycin into the vascular wall from a nonerodible polymeric stent coating in a range of doses (35-430 ug/5-18 mm coronary stent) produces a peak fifty to fifty-five percent reduction in neointimal hyperplasia as set forth in Table 3 below. This reduction, which is maximal at about twenty-eight to thirty days, is typically not sustained in the range of ninety to one hundred eighty days in the porcine model as set forth in Table 4 below.

TABLE 3.0

Animal Studies with Rapamycin-coated stents. Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm^2)	% Change From Polyme	Metal
Porcine							
98009	14 days	Metal		8	2.04 ± 0.17		
		1X + rapamycin	153 µg	8	1.66 ± 0.17*	-42%	-19%
		1X + TC300 + rapamycin	155 µg	8	1.51 ± 0.19*	-47%	-26%
99005	28 days	Metal		10	2.29 ± 0.21		
				9	3.91 ± 0.60**		
		1X + TC30 + rapamycin	130 µg	8	2.81 ± 0.34		+23%
		1X + TC100 + rapamycin	120 µg	9	2.62 ± 0.21		+14%
99006	28 days	Metal		12	4.57 ± 0.46		
		EVA/BMA 3X		12	5.02 ± 0.62		+10%
		1X + rapamycin	125 µg	11	2.84 ± 0.31* **	-43%	-38%
		3X + rapamycin	430 µg	12	3.06 ± 0.17* **	-39%	-33%
		3X + rapamycin	157 µg	12	2.77 ± 0.41* **	-45%	-39%
99011	28 days	Metal		11	3.09 ± 0.27		
				11	4.52 ± 0.37		
		1X + rapamycin	189 µg	14	3.05 ± 0.35		-1%
		3X + rapamycin/dex	182/363 µg	14	2.72 ± 0.71		-12%
99021	60 days	Metal		12	2.14 ± 0.25		
		1X + rapamycin	181 µg	12	2.95 ± 0.38		+38%
99034	28 days	Metal		8	5.24 ± 0.58		
		1X + rapamycin	186 µg	8	2.47 ± 0.33**		-53%
		3X + rapamycin/dex	185/369 µg	6	2.42 ± 0.64**		-54%
20001	28 days	Metal		6	1.81 ± 0.09		
		1X + rapamycin	172 µg	5	1.66 ± 0.44		-8%
20007							
	30 days	Metal		9	2.94 ± 0.43		
		1XTC + rapamycin	155 µg	10	1.40 ± 0.11*		-52%*
Rabbit							
99019	28 days	Metal		8	1.20 ± 0.07		

TABLE 3.0-continued

Animal Studies with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm²)	% Change From Polyme	% Change From Metal
		EVA/BMA 1X		10	1.26 ± 0.16		+5%
		1X + rapamycin	64 μg	9	0.92 ± 0.14	−27%	−23%
		1X + rapamycin	196 μg	10	0.66 ± 0.12* **	−48%	−45%
99020	28 days	Metal		12	1.18 ± 0.10		
		EVA/BMA 1X + rapamycin	197 μg	8	0.81 ± 0.16		−32%

[1]Stent nomenclature: EVA/BMA 1X, 2X, and 3X signifies approx. 500 μg, 1000 μg, and 1500 μg total mass (polymer + drug), respectively. TC, top coat of 30 μg, 100 μg, or 300 μg drug-free BMA; Biphasic; 2 × 1X layers of rapamycin in EVA/BMA spearated by a 100 μg drug-free BMA layer.
[2]0.25 mg/kg/d × 14 d preceeded by a loading dose of 0.5 mg/kg/d × 3 d prior to stent implantation.
*p < 0.05 from EVA/BMA control.
**p < 0.05 from Metal;
#Inflammation score: (0 = essentially no intimal involvement; 1 = <25% intima involved; 2 =≧25% intima involved; 3 = >50% intima involved).

TABLE 4.0

180 day Porcine Study with Rapamycin-coated stents.
Values are mean ± Standard Error of Mean

Study	Duration	Stent[1]	Rapamycin	N	Neointimal Area (mm²)	% Change From Polyme	% Change From Metal	Inflammation Score #
20007	3 days	Metal		10	0.38 ± 0.06			1.05 ± 0.06
(ETP-2-002233-P)		1XTC + rapamycin	155 μg	10	0.29 ± 0.03		−24%	1.08 ± 0.04
	30 days	Metal		9	2.94 ± 0.43			0.11 ± 0.08
		1XTC + rapamycin	155 μg	10	1.40 ± 0.11*		−52%*	0.25 ± 0.10
	90 days	Metal		10	3.45 ± 0.34			0.20 ± 0.08
		1XTC + rapamycin	155 μg	10	3.03 ± 0.29		−12%	0.80 ± 0.23
		1X + rapamycin	171 μg	10	2.86 ± 0.35		−17%	0.60 ± 0.23
	180 days	Metal		10	3.65 ± 0.39			0.65 ± 0.21
		1XTC + rapamycin	155 μg	10	3.34 ± 0.31		−8%	1.50 ± 0.34
		1X + rapamycin	171 μg	10	3.87 ± 0.28		+6%	1.68 ± 0.37

The release of rapamycin into the vascular wall of a human from a nonerodible polymeric stent coating provides superior results with respect to the magnitude and duration of the reduction in neointimal hyperplasia within the stent as compared to the vascular walls of animals as set forth above.

Humans implanted with a rapamycin coated stent comprising rapamycin in the same dose range as studied in animal models using the same polymeric matrix, as described above, reveal a much more profound reduction in neointimal hyperplasia than observed in animal models, based on the magnitude and duration of reduction in neointima. The human clinical response to rapamycin reveals essentially total abolition of neointimal hyperplasia inside the stent using both angiographic and intravascular ultrasound measurements. These results are sustained for at least one year as set forth in Table 5 below.

TABLE 5.0

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
Procedure Success (QCA)	100.0% (45/45)	[92.1%, 100.0%]
4-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	4.8% ± 6.1% (30)	[2.6%, 7.0%]
Range (min, max)	(−8.2%, 14.9%)	
6-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 7.6% (13)	[4.8%, 13.0%]
Range (min, max)	(−2.9%, 20.4%)	
12-month In-Stent Diameter Stenosis (%)		
Mean ± SD (N)	8.9% ± 6.1% (15)	[5.8%, 12.0%]
Range (min, max)	(−3.0%, 22.0%)	

TABLE 5.0-continued

Patients Treated (N = 45 patients) with a Rapamycin-coated Stent

Effectiveness Measures	Sirolimus FIM (N = 45 Patients, 45 Lesions)	95% Confidence Limit
4-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.00 ± 0.29 (30)	[-0.10, 0.10]
Range (min, max)	(-0.51, 0.45)	
6-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.25 ± 0.27 (13)	[0.10, 0.39]
Range (min, max)	(-0.51, 0.91)	
12-month In-Stent Late Loss (mm)		
Mean ± SD (N)	0.11 ± 0.36 (15)	[-0.08, 0.29]
Range (min, max)	(-0.51, 0.82)	
4-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	10.48% ± 2.78% (28)	[9.45%, 11.51%]
Range (min, max)	(4.60%, 16.35%)	
6-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	7.22% ± 4.60% (13)	[4.72%, 9.72%],
Range (min, max)	(3.82%, 19.88%)	
12-month Obstruction Volume (%) (IVUS)		
Mean ± SD (N)	2.11% ± 5.28% (15)	[0.00%, 4.78%],
Range (min, max)	(0.00%, 19.89%)	
6-month Target Lesion Revascularization (TLR)	0.0% (0/30)	[0.0%, 9.5%]
12-month Target Lesion Revascularization (TLR)	0.0% (0/15)	[0.0%, 18.1%]

QCA = Quantitative Coronary Angiography
SD = Standard Deviation
IVUS = Intravascular Ultrasound

Rapamycin produces an unexpected benefit in humans when delivered from a stent by causing a profound reduction in in-stent neointimal hyperplasia that is sustained for at least one year. The magnitude and duration of this benefit in humans is not predicted from animal model data. Rapamycin used in this context includes rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin.

These results may be due to a number of factors. For example, the greater effectiveness of rapamycin in humans is due to greater sensitivity of its mechanism(s) of action toward the pathophysiology of human vascular lesions compared to the pathophysiology of animal models of angioplasty. In addition, the combination of the dose applied to the stent and the polymer coating that controls the release of the drug is important in the effectiveness of the drug.

As stated above, rapamycin reduces vascular hyperplasia by antagonizing smooth muscle proliferation in response to mitogenic signals that are released during angioplasty injury. Also, it is known that rapamycin prevents T-cell proliferation and differentiation when administered systemically. It has also been determined that rapamycin exerts a local inflammatory effect in the vessel wall when administered from a stent in low doses for a sustained period of time (approximately two to six weeks). The local anti-inflammatory benefit is profound and unexpected. In combination with the smooth muscle anti-proliferative effect, this dual mode of action of rapamycin may be responsible for its exceptional efficacy.

Accordingly, rapamycin delivered from a local device platform, reduces neointimal hyperplasia by a combination of anti-inflammatory and smooth muscle anti-proliferative effects. Rapamycin used in this context means rapamycin and all analogs, derivatives and congeners that bind FKBP12 and possess the same pharmacologic properties as rapamycin. Local device platforms include stent coatings, stent sheaths, grafts and local drug infusion catheters or porous balloons or any other suitable means for the in situ or local delivery of drugs, agents or compounds.

The anti-inflammatory effect of rapamycin is evident in data from an experiment, illustrated in Table 6, in which rapamycin delivered from a stent was compared with dexamethasone delivered from a stent. Dexamethasone, a potent steroidal anti-inflammatory agent, was used as a reference standard. Although dexamethasone is able to reduce inflammation scores, rapamycin is far more effective than dexamethasone in reducing inflammation scores. In addition, rapamycin significantly reduces neointimal hyperplasia, unlike dexamethasone.

TABLE 6.0

Group Rapamycin Rap	N=	Neointimal Area (mm^2)	% Area Stenosis	Inflammation Score
Uncoated	8	5.24 ± 1.65	54 ± 19	0.97 ± 1.00
Dexamethasone (Dex)	8	4.31 ± 3.02	45 ± 31	0.39 ± 0.24
Rapamycin (Rap)	7	2.47 ± 0.94*	26 ± 10*	0.13 ± 0.19*
Rap + Dex	6	2.42 ± 1.58*	26 ± 18*	0.17 ± 0.30*

*= significance level $P < 0.05$

Rapamycin has also been found to reduce cytokine levels in vascular tissue when delivered from a stent. The data in FIG. 1 illustrates that rapamycin is highly effective in reducing monocyte chemotactic protein (MCP-1) levels in

the vascular wall. MCP-1 is an example of a proinflammatory/chemotactic cytokine that is elaborated during vessel injury. Reduction in MCP-1 illustrates the beneficial effect of rapamycin in reducing the expression of proinflammatory mediators and contributing to the anti-inflammatory effect of rapamycin delivered locally from a stent. It is recognized that vascular inflammation in response to injury is a major contributor to the development of neointimal hyperplasia.

Since rapamycin may be shown to inhibit local inflammatory events in the vessel it is believed that this could explain the unexpected superiority of rapamycin in inhibiting neointima.

As set forth above, rapamycin functions on a number of levels to produce such desired effects as the prevention of T-cell proliferation, the inhibition of negative remodeling, the reduction of inflammation, and the prevention of smooth muscle cell proliferation. While the exact mechanisms of these functions are not completely known, the mechanisms that have been identified may be expanded upon.

Studies with rapamycin suggest that the prevention of smooth muscle cell proliferation by blockade of the cell cycle is a valid strategy for reducing neointimal hyperplasia. Dramatic and sustained reductions in late lumen loss and neointimal plaque volume have been observed in patients receiving rapamycin delivered locally from a stent. The present invention expands upon the mechanism of rapamycin to include additional approaches to inhibit the cell cycle and reduce neointimal hyperplasia without producing toxicity.

The cell cycle is a tightly controlled biochemical cascade of events that regulate the process of cell replication. When cells are stimulated by appropriate growth factors, they move from G_0 (quiescence) to the G1 phase of the cell cycle. Selective inhibition of the cell cycle in the G1 phase, prior to DNA replication (S phase), may offer therapeutic advantages of cell preservation and viability while retaining anti-proliferative efficacy when compared to therapeutics that act later in the cell cycle i.e. at S, G2 or M phase.

Accordingly, the prevention of intimal hyperplasia in blood vessels and other conduit vessels in the body may be achieved using cell cycle inhibitors that act selectively at the G1 phase of the cell cycle. These inhibitors of the G1 phase of the cell cycle may be small molecules, peptides, proteins, oligonucleotides or DNA sequences. More specifically, these drugs or agents include inhibitors of cyclin dependent kinases (cdk's) involved with the progression of the cell cycle through the G1 phase, in particular cdk2 and cdk4.

Examples of drugs, agents or compounds that act selectively at the G1 phase of the cell cycle include small molecules such as flavopiridol and its structural analogs that have been found to inhibit cell cycle in the late G1 phase by antagonism of cyclin dependent kinases. Therapeutic agents that elevate an endogenous kinase inhibitory protein^{kip} called P27, sometimes referred to as P27^{kip1}, that selectively inhibits cyclin dependent kinases may be utilized. This includes small molecules, peptides and proteins that either block the degradation of P27 or enhance the cellular production of P27, including gene vectors that can transfact the gene to produce P27. Staurosporin and related small molecules that block the cell cycle by inhibiting protein kinases may be utilized. Protein kinase inhibitors, including the class of tyrphostins that selectively inhibit protein kinases to antagonize signal transduction in smooth muscle in response to a broad range of growth factors such as PDGF and FGF may also be utilized.

Any of the drugs, agents or compounds discussed above may be administered either systemically, for example,

orally, intravenously, intramuscularly, subcutaneously, nasally or intradermally, or locally, for example, stent coating, stent covering or local delivery catheter. In addition, the drugs or agents discussed above may be formulated for fast-release or slow release with the objective of maintaining the drugs or agents in contact with target tissues for a period ranging from three days to eight weeks.

As set forth above, the complex of rapamycin and FKPB12 binds to and inhibits a phosphoinositide (PI)-3 kinase called the mammalian Target of Rapamycin or TOR. An antagonist of the catalytic activity of TOR, functioning as either an active site inhibitor or as an allosteric modulator, i.e. an indirect inhibitor that allosterically modulates, would mimic the actions of rapamycin but bypass the requirement for FKBP12. The potential advantages of a direct inhibitor of TOR include better tissue penetration and better physical/chemical stability. In addition, other potential advantages include greater selectivity and specificity of action due to the specificity of an antagonist for one of multiple isoforms of TOR that may exist in different tissues, and a potentially different spectrum of downstream effects leading to greater drug efficacy and/or safety.

The inhibitor may be a small organic molecule (approximate mw<1000), which is either a synthetic or naturally derived product. Wortmanin may be an agent which inhibits the function of this class of proteins. It may also be a peptide or an oligonucleotide sequence. The inhibitor may be administered either sytemically (orally, intravenously, intramuscularly, subcutaneously, nasally, or intradermally) or locally (stent coating, stent covering, local drug delivery catheter). For example, the inhibitor may be released into the vascular wall of a human from a nonerodible polymeric stent coating. In addition, the inhibitor may be formulated for fast-release or slow release with the objective of maintaining the rapamycin or other drug, agent or compound in contact with target tissues for a period ranging from three days to eight weeks.

As stated previously, the implantation of a coronary stent in conjunction with balloon angioplasty is highly effective in treating acute vessel closure and may reduce the risk of restenosis. Intravascular ultrasound studies (Mintz et al., 1996) suggest that coronary stenting effectively prevents vessel constriction and that most of the late luminal loss after stent implantation is due to plaque growth, probably related to neointimal hyperplasia. The late luminal loss after coronary stenting is almost two times higher than that observed after conventional balloon angioplasty. Thus, inasmuch as stents prevent at least a portion of the restenosis process, the use of drugs, agents or compounds which prevent inflammation and proliferation, or prevent proliferation by multiple mechanisms, combined with a stent may provide the most efficacious treatment for post-angioplasty restenosis.

The local delivery of drugs, agents or compounds from a stent has the following advantages; namely, the prevention of vessel recoil and remodeling through the scaffolding action of the stent and the drugs, agents or compounds and the prevention of multiple components of neointimal hyperplasia. This local administration of drugs, agents or compounds to stented coronary arteries may also have additional therapeutic benefit. For example, higher tissue concentrations would be achievable than that which would occur with systemic administration, reduced systemic toxicity, and single treatment and ease of administration. An additional benefit of drug therapy may be to reduce the dose of the therapeutic compounds, thereby limiting their toxicity, while still achieving a reduction in restenosis.

There are a multiplicity of different stents that may be utilized following percutaneous transluminal coronary angioplasty. Although any number of stents may be utilized in accordance with the present invention, for simplicity, one particular stent will be described in exemplary embodiments of the present invention. The skilled artisan will recognize that any number of stents may be utilized in connection with the present invention.

A stent is commonly used as a tubular structure left inside the lumen of a duct to relieve an obstruction. Commonly, stents are inserted into the lumen in a non-expanded form and are then expanded autonomously, or with the aid of a second device in situ. A typical method of expansion occurs through the use of a catheter-mounted angioplasty balloon which is inflated within the stenosed vessel or body passageway in order to shear and disrupt the obstructions associated with the wall components of the vessel and to obtain an enlarged lumen. As set forth below, self-expanding stents may also be utilized.

FIG. **2** illustrates an exemplary stent **100** which may be utilized in accordance with an exemplary embodiment of the present invention. The expandable cylindrical stent **100** comprises a fenestrated structure for placement in a blood vessel, duct or lumen to hold the vessel, duct or lumen open, more particularly for protecting a segment of artery from restenosis after angioplasty. The stent **100** may be expanded circumferentially and maintained in an expanded configuration, that is circumferentially or radially rigid. The stent **100** is axially flexible and when flexed at a band, the stent **100** avoids any externally-protruding component parts.

The stent **100** generally comprises first and second ends with an intermediate section therebetween. The stent **100** has a longitudinal axis and comprises a plurality of longitudinally disposed bands **102**, wherein each band **102** defines a generally continuous wave along a line segment parallel to the longitudinal axis. A plurality of circumferentially arranged links **104** maintain the bands **102** in a substantially tubular structure. Essentially, each longitudinally disposed band **102** is connected at a plurality of periodic locations, by a short circumferentially arranged link **104** to an adjacent band **102**. The wave associated with each of the bands **102** has approximately the same fundamental spatial frequency in the intermediate section, and the bands **102** are so disposed that the wave associated with them are generally aligned so as to be generally in phase with one another. As illustrated in the figure, each longitudinally arranged band **102** undulates through approximately two cycles before there is a link to an adjacent band.

The stent **100** may be fabricated utilizing any number of methods. For example, the stent **100** may be fabricated from a hollow or formed stainless steel tube that may be machined using lasers, electric discharge milling, chemical etching or other means. The stent **100** is inserted into the body and placed at the desired site in an unexpanded form. In one embodiment, expansion may be effected in a blood vessel by a balloon catheter, where the final diameter of the stent **100** is a function of the diameter of the balloon catheter used.

It should be appreciated that a stent **100** in accordance with the present invention may be embodied in a shape-memory material, including, for example, an appropriate alloy of nickel and titanium. In this embodiment, after the stent **100** has been formed it may be compressed so as to occupy a space sufficiently small as to permit its insertion in a blood vessel or other tissue by insertion means, wherein the insertion means include a suitable catheter, or flexible rod. On emerging from the catheter, the stent **100** may be configured to expand into the desired configuration where the expansion is automatic or triggered by a change in pressure, temperature or electrical stimulation.

FIG. **3** illustrates an exemplary embodiment of the present invention utilizing the stent **100** illustrated in FIG. **2**. As illustrated, the stent **100** may be modified to comprise a reservoir **106**. Each of the reservoirs may be opened or closed as desired. These reservoirs **106** may be specifically designed to hold the drug, agent, compound or combinations thereof to be delivered. Regardless of the design of the stent **100**, it is preferable to have the drug, agent, compound or combinations thereof dosage applied with enough specificity and a sufficient concentration to provide an effective dosage in the lesion area. In this regard, the reservoir size in the bands **102** is preferably sized to adequately apply the drug/drug combination dosage at the desired location and in the desired amount.

In an alternate exemplary embodiment, the entire inner and outer surface of the stent **100** may be coated with various drug and drug combinations in therapeutic dosage amounts. A detailed description of exemplary coating techniques is described below.

Rapamycin or any of the drugs, agents or compounds described above may be incorporated into or affixed to the stent in a number of ways and utilizing any number of biocompatible materials. In the exemplary embodiment, the rapamycin is directly incorporated into a polymeric matrix and sprayed onto the outer surface of the stent. The rapamycin elutes from the polymeric matrix over time and enters the surrounding tissue. The rapamycin preferably remains on the stent for at least three days up to approximately six months and more preferably between seven and thirty days.

Any number of non-erodible polymers may be utilized in conjunction with rapamycin. In the exemplary embodiment, the polymeric matrix comprises two layers. The base layer comprises a solution of ethylene-co-vinylacetate and polybutylmethacrylate. The rapamycin is incorporated into this layer. The outer layer comprises only polybutylmethacrylate and acts as a diffusion barrier to prevent the rapamycin from eluting too quickly and entering the surrounding tissues. The thickness of the outer layer or top coat determines the rate at which the rapamycin elutes from the matrix. Essentially, the rapamycin elutes from the matrix by diffusion through the polymer molecules. Polymers tend to move, thereby allowing solids, liquids and gases to escape therefrom. The total thickness of the polymeric matrix is in the range from about 1 micron to about 20 microns or greater. In a preferred exemplary embodiment, the base layer, including the polymer and drug, has a thickness in the range from about 8 microns to about 12 microns and the outer layer has a thickness in the range from about 1 micron to about 2 microns.

The ethylene-co-vinylacetate, polybutylmethacrylate and rapamycin solution may be incorporated into or onto the stent in a number of ways. For example, the solution may be sprayed onto the stent or the stent may be dipped into the solution. In a preferred embodiment, the solution is sprayed onto the stent and then allowed to dry. In another exemplary embodiment, the solution may be electrically charged to one polarity and the stent electrically changed to the opposite polarity. In this manner, the solution and stent will be attracted to one another. In using this type of spraying process, waste may be reduced and more control over the thickness of the coat may be achieved.

Since rapamycin works by entering the surrounding tissue, it is preferably only affixed to the surface of the stent making contact with one tissue. Typically, only the outer surface of the stent makes contact with the tissue. Accord-

ingly, in a preferred embodiment, only the outer surface of the stent is coated with rapamycin. For other drugs, agents or compounds, the entire stent may be coated.

It is important to note that different polymers may be utilized for different stents. For example, in the above-described embodiment, ethylene-co-vinylacetate and polybutylmethacrylate are utilized to form the polymeric matrix. This matrix works well with stainless steel stents. Other polymers may be utilized more effectively with stents formed from other materials, including materials that exhibit superelastic properties such as alloys of nickel and titanium.

Although shown and described is what is believed to be the most practical and preferred embodiments, it is apparent that departures from specific designs and methods described and shown will suggest themselves to those skilled in the art and may be used without departing from the spirit and scope of the invention. The present invention is not restricted to the particular constructions described and illustrated, but should be constructed to cohere with all modifications that may fall within the scope of the appended claims.

What is claimed is:

1. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides an in-stent late loss in diameter at 12 months following implantation in a human of less than about 0.5 mm, as measured by quantitative coronary angiography.

2. A drug delivery device according to claim 1 that provides an in- stent late loss in diameter at 12 months following implantation in a human of less than about 0.3 mm, as measured by quantitative coronary angiography.

3. A drug delivery device according to claim 1 or 2 that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 22%, as measured by quantitative coronary angiography.

4. A drug delivery device according to claim 3 that provides an in-stent diameter stenosis at 12 months following implantation in a human of less than about 15%, as measured by quantitative coronary angiography.

5. A drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said device provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

6. A drug delivery device according to claim 5 that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

7. A drug delivery device according to claim 5 or 6 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

8. A drug delivery device according to claim 7 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

9. A method of inhibiting neointimal proliferation in a human coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

10. A method according to claim 9 that provides an in-stent late loss in diameter at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

11. A method according to claim 9 or 10 that provides an in-stent diameter stenosis at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

12. A method according to claim 11 that provides an in-stent diameter stenosis at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

13. A method of inhibiting neointimal proliferation in a coronary artery resulting from percutaneous transluminal coronary angioplasty comprising implanting in the lumen of said coronary artery a drug delivery device comprising: an intraluminal stent; a biocompatible, nonerodible polymeric coating affixed to the intraluminal stent; and from about 64 μg to about 197 μg of rapamycin or a macrocyclic triene analog thereof that binds FKBP12 incorporated into the polymeric coating, wherein said method provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.5 mm, as measured by quantitative coronary angiography.

14. A method according to claim 13 that provides a mean in-stent late loss in diameter in a human population at 12 months following implantation of less than about 0.3 mm, as measured by quantitative coronary angiography.

15. A method according to claim 13 or 14 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 22%, as measured by quantitative coronary angiography.

16. A method according to claim 15 that provides a mean in-stent diameter stenosis in a human population at 12 months following implantation of less than about 15%, as measured by quantitative coronary angiography.

17. The drug delivery device according to any one of claims 1, 2, 4 or 5 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

18. The drug delivery device according to to any one of claims 1, 2, 4 or 5 that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

19. The drug delivery device according to any one of claims 1, 2, 4 or 5 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

20. The drug delivery device according to claim 19 wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

21. The drug delivery device according to claim 19 that releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

22. The method according to any one of claims 9, 10, 13 or 14, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 64 μg to about 125 μg.

23. The method according to any one of claims 9, 10, 13 or 14, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 2 μg to about 30 μg per millimeter of stent length.

24. The method according to any one of claims 9, 10, 13 or 14, wherein said rapamycin or macrocyclic triene analog thereof is incorporated into the polymeric coating at a dose of from about 3 μg to about 13 μg per millimeter of stent length.

25. The method according to any one of claims 9, 10, 13 or 14, wherein said drug delivery device releases a portion of said dose of rapamycin or a macrocyclic triene analog thereof at about six weeks following intraluminal implantation.

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